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Acute perforated peptic ulcer: evaluation of 160 consecutive patients treated by closure

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Acute perforation of a peptic ulcer continues to be one of the major life-threatening complications associated with the disease. Early recognition and proper management of this catastrophe save lives and reduce the period of disability.

The method of treatment continues to remain controversial, whether operative or nonoperative. However, a greater swing to operative closure as the method of choice has been apparent again in recent years. There remain a few advocates of the nonoperative method of treatment. Selectivity and a certain percentage of cases in which the diagnosis is incorrect may definitely influence their favorable results and effect the low mortality rate reported.

There are a number of critical reasons against nonoperative management of patients with acute perforations; (1) aspiration rarely is completely successful in stomachs full of either food or liquids, (2) large lesions rarely seal, (3) occasionally the tip of the aspirating tube passes through the perforation, (4) food particles may temporarily plug the perforation and healing will not occur, (5) a number of so-called "successfully treated" ulcers are actually penetrating and not perforated, (6) without operation there is always the danger of a missed diagnosis with involvement of another organ for which operation was necessary, (7) perforation due to malignancy is possible and without operation may go undiagnosed, and (8) bed rest may well delay definitive operation until it cannot safely be performed.

This is a presentation of the results of the surgical management of acute perforations of peptic ulcer in 160 unselected and consecutively treated patients admitted to our hospital from Jan. 1, 1946, to Jan. 1, 1960. A comparison of these results will be made with results in a series of 56 consecutively treated and unselected patients we reported upon in 1953.

It was our opinion then, and still is, that improvement can be expected in the surgical management of these patients by the judicious use of antibiotics, better application of anesthesiology, coordinated and balanced pre- and postoperative care, earlier surgical closure of the perforation and, in a care-

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Table I. *Age incidence*

Age (yr.)	*1953 report*		*Present 14 yr. report*	
	No.	*%*	*No.*	*%*
20-30	8	14.0	13	8
31-40	20	36.0	48	30
41-50	6	11.0	46	29
51-60	15	27.0	42	27
61-70	6	10.2	7	4
Over 70	1	1.8	4	2
Totals	56		160	

fully selected group, primary definitive operation at the time of perforation, and finally the establishment of an early "planned definitive resection" at an early date after simple closure. Such planning is accomplished with patient's cooperation and can usually be performed several weeks after preliminary closure. The latter procedure is used to prevent repeated perforations and other serious later complications which cause prolonged periods of disability and life-threatening hazards which lead to greater surgical risks and increased morbidity and mortality rates.

The series of 160 cases* reported represents a controlled group studied under the guidance and direction of one Chief of the Surgical Service (L.T.P.). The rationale of therapy, criteria for operation, and method of management were consistently controlled.

RESULTS

The patients ranged in age from 21 to 78 years, and the average age was 47.2 years. Approximately 85 per cent of the patients in this series were in the 3 decades after the age of 31 years. Comparison with our earlier paper[1] shows changes, the significance of which may be simply that these decades usually contain the major number of patients with duodenal ulcer and its complications (Table I).

The average time which elapsed from perforation to operation was nearly 9 hours (Table II). The shortest time was less than 3 hours; all of the 5 patients in this group were in the hospital at the time of perforation. All 5 had suffered typical ulcer distress periodically for years. Three had been hospitalized for other complaints when perforation occurred.

The longest time interval was 120 hours and 17 (10.6 per cent) of the entire group showed a total elapsed time from perforation to operation of over 24 hours. There were 98 patients (62.2 per cent) operated upon in less than 6 hours. In a group of 30 (18.75 per cent), operation was delayed more than 6 but less than 12 hours. Finally patients operated upon after 12 and after 18 hours (but before 24 hours) were 9 (5.6 per cent) and 6 (3.75 per cent), respectively.

Table III illustrates a fact of which surgeons have long been aware–that there is a long delay before a patient seeks medical attention and/or is admitted to a hospital for definitive surgical care.

There were 5 patients, not listed in Table III, whom we operated upon within 3 hours from the time of perforation. This is considered an ideal time and represents a reasonable period in which to admit the patient, treat him, and prepare him for operation.

Table II. *Total time interval between perforation and operation*

Time interval (hr.)	*No. of patients*	*%*
0- 3	5	3.1
0- 6	93	58.1
7-12	30	18.8
13-18	9	5.6
19-24	6	3.8
Over 24	17	10.6
Totals	160	100

Table III. *Time elapsed from perforation to hospitalization*

Time interval (hr.)	*No. of patients*	*%*
0- 6	93	60.0
7-12	30	19.4
13-18	9	5.8
19-24	6	3.8
Over 24	17	11.0

*These patients will be included in a cooperative peptic ulcer study which the Veterans Administration Research in Surgery is conducting.

Table IV. *Time interval from perforation to operation by age groups*

Age groups (yr.)	*Time interval (hr.)*		
	Average	*Longest*	*Shortest*
21-30	24.2	120.0	4
31-40	7.4	34.0	3
41-50	9.4	32.0	3
51-60	8.6	18.2	3
61-70	10.5	11.0	3
Over 70	6.8	7.2	5

Table IV provides a breakdown of patients by age groups and time interval between perforation and operation. The longest period of delay occurs in the youngest age group (21 to 30 years).

The average duration of symptoms in patients in this entire series, from whom a definite history could be obtained, was 6.3 years. In 41 patients (25.6 per cent) a so-called "silent" ulcer was noted. However, by closer evaluation of the patients' records the "silent" ulcer group was only 9.3 per cent. Over 56 per cent of all the patients developed perforation after a spree of immoderate use of alcohol. Bleeding occurred just prior to the perforation in 40 patients (25 per cent). The remaining 14 patients all had undergone a previous operation for perforation.

PREOPERATIVE STUDIES AND TREATMENT

During the past 4 years no chemicals or antibiotics were introduced into the peritoneal cavity at the time of operation. The use of neomycin was stopped immediately when we observed and read in the literature of the untoward reaction that occurs when curare as an anesthetic agent is used with other anesthetic agents–a depression of respiratory exchange caused by central toxic action in the brain. In fact, in the last 7 years, the usual procedure has been to evacuate as much as possible of the collected fluid and material from the peritoneal cavity. If such soilage was extensive, then saline irrigation or, if believed necessary, irrigation with penicillin and/or streptomycin was employed prior to closure of the wound to lessen the possibility of local collection of irritants and prevent abscess formation.

ANESTHESIA AND CLOSURE

Practically all the patients were given inhalation anesthesia. A short right transverse incision (154 cases) above the umbilicus, dividing the right anterior and posterior rectus sheaths transversely, was performed. The right rectus muscle was transected.

During the early years, the wound closure was accomplished with catgut in 37 cases, or 23 per cent of the group. In 115 patients (72 per cent) silk was used; wire was used in only 8 patients (5 per cent). There were only 3 wound infections, none of which were severe. This represents an incidence of only 1.8 per cent. One infection (2.7 per cent) occurred in the early group with catgut closure; in the group with silk closure there was only 1 wound infection (0.8 per cent) and in the small group with wire closure there was 1 infection (12.5 per cent).

There were no instances of wound dehiscence or postoperative herniation.

LOCATION OF ULCER

In the entire series of 160 patients, 119 (74.4 per cent) had perforation of an anterior duodenal ulcer involving the first part of the duodenum. In 26 (16.2 per cent) the perforation was of a gastric ulcer or lesion. There were 15 patients (9.4 per cent) with perforations in the obscure area of the "pyloric canal."

If there existed any question that the perforation might be of gastric origin, a biopsy specimen was taken, as it was in most instances of definite gastric perforation. No evidence of adenocarcinoma of the stomach was found. In only 1 instance was a malignancy found; this finally proved to be a lymphosarcoma. Gastric resection was performed and the patient had no evidence of recurrence of lesion at the time of his accidental death 7 years later.

CLOSURE

Simple closure of the perforation was performed in 153 patients (95.6 per cent).

This was accomplished by the use of interrupted Lembert sutures, incorporating an omental pedicle as reinforcement. In 2 patients (1.25 per cent) it was necessary to use a purse-string suture of catgut, reinforced by interrupted Lembert sutures, again with an omental pedicle graft. In 2 other patients, the defect was so large and the accompanying edema and friability of the tissue so great that an attempt at the usual closure would have resulted in pyloric obstruction postoperatively. In both instances the round ligaments of the liver and omentum were used as patches.

In the entire 14 years there were only 3 patients (1.9 per cent) for whom we were of the opinion that primary gastric resection was indicated at the time of acute duodenal perforation. In all 3 the operation was performed within 6 hours from the time of perforation and the other conditions were met from the standpoint of pathologic process, ulcer history, obstruction, minimal peritoneal spillage, and chemical peritonitis, and the general condition of the patients was excellent.

MORTALITY RATE

There were no deaths in the entire series.

POSTOPERATIVE TREATMENT

The patients treated during the 1946 to 1948 period were ambulatory on the second to the fourth postoperative day. After 1948, all patients were ambulatory on the first day.

Nasogastric suction was continued for from 2 to 3 days postoperatively in the group of patients without complications. Oral feedings were started on the third to the fifth postoperative day. The patient then received a progressive gastric diet.

EARLY POSTOPERATIVE COMPLICATIONS

Early postoperative complications (Table V) developed in 23 patients (14.3 per cent). This represents a 50 per cent decrease when the current 104 patients were compared. All postoperative gastric hemorrhages were completely controlled by conservative management. Patients with pyloric obstruction did well after planned early definitive resection. The other complications listed in Table V required only treatment ordinarily accorded the specific disease or condition.

HOSPITAL STAY

In the entire previous group of 56 patients, those without serious complications were discharged from the hospital by the sixteenth postoperative day. They were recalled 28 days later for any necessary study and treatment. Those without complaints or complications were then treated medically.

In the later group, particularly in the last 5 years, definitive surgical treatment for chronic duodenal ulcer was strongly recommended. If the patient did not accept it, he was discharged and recalled for follow-up study at regular intervals. In recent years this recall system has produced a follow-up of over 90 per cent of patients studied.

Table V. *Early postoperative complications*

Type	*First group (56 patients)*		*Second group (104 patients)*		*Total 160 patients*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Abscess, pelvic	1	1.8	1	0.9	2	1.2
Abscess, subhepatic	0	0	1	0.9	1	0.6
Cardiac decompensation	1	1.8	1	0.9	2	1.2
Distention, severe	1	1.8	1	0.9	2	1.2
Effusion, pleural	1	1.8	0	0	1	0.6
Hemorrhage, gastrointestinal	3	5.3	2	1.9	5	3.1
Infection, wound	1	1.8	2	1.9	3	1.8
Obstruction, pyloric	3	5.3	3	2.8	6	3.7
Perforation, esophageal	1	1.8	0	0	1	0.6
Totals	12	21.4	11	10.2	23	14.0

RESULTS AND RATE OF RETURN FOR FOLLOW-UP

The longest period of follow-up was 13 years and the shortest period was 13 months. The average period of follow-up was 9.5 years with a follow-up rate of 91.3 per cent, or 146 patients. Failure to follow the remaining 14 patients was due to the fact several had moved from our area, and in a few instances no replies could be obtained from our inquiries.

EVALUATION OF FINAL RESULTS

Of the 143 patients remaining with adequate follow-up studies, 4 classifications of their progress was easily made; (1) patients for whom medical management alone was sufficient, with no symptoms or signs of trouble, and with normal roentgenographic findings (31 patients, 21.7 per cent), (2) patients still under medical management who demonstrated symptoms or signs of recurring ulceration, obstruction, or bleeding in whom the clinical findings were confirmed roentgenographically and for whom further surgical intervention seemed inevitable (23 patients, 16 per cent), (3) patients who already had undergone gastric operation for reasons not associated with the original duodenal ulcer (2 patients, 1.4 per cent), and (4) patients who developed one or more of the classic complications of duodenal ulcer or benign gastric ulcer which necessitated further definitive gastric operations for relief (87 patients, 60.8 per cent).

COMMENT

Primary early closure of acute peptic ulcer perforation in our hands remains the procedure of choice and results in a minimal morbidity and disability. The advocates of the nonoperative treatment of this type of patient have not met these criteria and our results.

It is our opinion that immediate definitive operation at the time of perforation has its place, but certainly is limited to a select group of patients under rigid indications. The prime tenet is to perform the simplest and safest procedure to save life with the least disablement and to plan a careful and repeated follow-up for selection and preparation of the patient for early "planned definitive gastric operation."

The greatest weakness in the past in most series has been the loss of follow-up and control of the patient who experienced a perforated peptic ulcer. It is difficult to assess accurately the actual number who develop the late serious complications of peptic ulcer disease which necessitate surgical intervention. With the program that we have evolved in the past 5 years, we are able now to predict with some degree of accuracy the number of patients who will need operations after perforation. Therefore, we can anticipate sooner the need for definitive procedures in patients whom we follow and thus recommend to them early elective antrectomy with vagectomy.

The prognosis can be greatly influenced by early surgical closure of a perforation. The interval of time between perforation and closure still remains the most lethal factor. A reduction in this time rests in the hands of both the patient and his physician. Too often, however, the patient himself or his family are responsible for this delay. Frequently the patient is referred for consultation late. Any educational program that will aid in the earlier seeking of medical attention, earlier recognition of the acute emergency, speedier and better preoperative preparation of the patient, coupled with all the advances previously mentioned, will result in continued improvement with further reduction in the morbidity and mortality rates.

The public would benefit even more when realization of the emergency nature of this catastrophe is accepted. Early diagnosis and insistence upon prompt emergency hospitalization regardless of transportation, family, and other conflicts are key factors.

It is important to note that over 60 per cent of the patients in this series, to date, have already undergone definitive gastric operations and that 16 per cent currently are experiencing difficulty from one or more of the complications from chronic ulceration.

SUMMARY AND CONCLUSIONS

The results of the emergency operative treatment of acute perforated peptic ulcer in 160 consecutively treated male patients are presented. There were no deaths. The patients ranged in age from 21 to 78 years. The average time interval from acute perforation to surgical closure of defect was 9 hours. A small transverse right supraumbilical incision was employed. Silk suture closure of the wound was accomplished. Dehiscence and postoperative herniation did not occur. Neither the peritoneal cavity nor the wound was drained. There were only 3 wound infections (1.8 per cent), and 1 pelvic abscess and 1 subhepatic abscess occurred.

By carefully controlled, early follow-up program, early definitive elective gastric operation was recommended and performed in 60 per cent of the patients in this series to date. This was necessary because of the progressive complications associated with chronic duodenal ulcer. At this time there are an additional 16 per cent who also need definitive operations.

Therefore, in the past several years there has not been an abandonment of our former position that the simple surgical closure procedure is a life-saving emergency measure, that it should be performed early and quickly, that education of the public and members of the profession concerning the harmful effects of delay is mandatory, and that all patients and their families be indoctrinated from the first that very probably 2 procedures requiring 2 separate operations will be necessary. Early planned "definitive gastric operation" in a high per cent of these patients will result in a marked decrease in disability, chronic invalidism, and the many later complications associated with a chronic ulcer diathesis.

REFERENCE

1. Palumbo, L. T., and Rugtiv, G. M.: Results of operative treatment of acute perforated peptic ulcer, SURGERY **34:** 635, 1953.

Renal function during and immediately after profound hypothermia

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Although the body is able to make certain adjustments to changing circumstances in order to maintain a satisfactory "milieu interior," such adjustments are not necessarily always favorable. Surgical techniques employed to improve operative conditions in certain organs may evoke responses in others which are perhaps detrimental, and a sound knowledge of such concomitant responses is essential. Only when it is clear that the beneficial effects of these techniques outweigh the dangerous responses can their use be justified.

With the increased use of profound levels of hypothermia in cardiac, brain, and vascular operations, a careful study of the responses of the body to the sudden reduction in temperature that occurs seems justified. This report concerns the changes in certain renal functions observed during and after cardiopulmonary bypass with profound hypothermia.

METHODS

Operative and bypass procedure. Nine healthy adult mongrel dogs which weighed between 15 and 21 kilograms were anesthetized intravenously with thiopental sodium and after intubation anesthesia was maintained with nitrous oxide and oxygen. Polyethylene cannulas were inserted into the left femoral artery and vein and connected to manometers for pressure recordings. One needle was inserted into a vein in one of the forelimbs and a second into a vein in the right hindlimb for intravenous infusions during the experiments.

In 7 of the dogs, profound hypothermia was induced, and in these the heart was approached by a left thoracotomy through the fourth intercostal space. In the 2 control dogs, in which the renal functions were studied under normothermic conditions, the heart was exposed through a right thoracotomy.

After intravenous systemic heparinization with 1.5 mg. of heparin per kilogram of body weight, the right common femoral artery was exposed and catheterized with a stainless steel catheter. The arterial line of the helix reservoir bubble oxygenator,[6, 7, 12] which had been previously assembled[2, 12] and primed[13] with heparinized donor blood, was connected to the arterial catheter. Bennington heat exchange units* were incorporated in the arterial line when hypothermia was to be induced.[25]

In the 7 hypothermic dogs, the venous blood was drained by means of a single No. 32 Bardex catheter introduced into the right atrium through the right atrial appendage; once hypothermic failure of the heart had occurred, a second catheter was introduced into the left atrium through the left atrial appendage, and the blood aspirated from the

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*Supplied by Westdene Products (Pty) Ltd., Cape Town, South Africa.

left heart was returned to the heart-lung machine in this manner. In the 2 control dogs, the venous blood was drained by means of catheters in the superior and inferior venae cavae.

Flow rates of 70 ml. per kilogram of body weight per minute were maintained throughout the perfusions of all the animals except Dog 1, in which extracorporeal circulation was stopped completely for 30 minutes during the cold phase. No cardiac operation was performed during any of these experiments. Rectal and esophageal temperatures were recorded in the dogs by means of the electric universal thermometer type TE-3, with leads types R-7 and OSG-1.*

At the end of the perfusion, when a normal heartbeat had been established, bypass was discontinued in the conventional manner. The heparin was neutralized with the required amount of protamine sulphate and blood deficit was replaced through the arterial catheter with arterial and venous pressures as monitors.

The wounds were closed and a chest drain was attached to a suction apparatus. The dogs were then returned to a warm recovery cage. No special postoperative care, apart from overnight intravenous administration of fluids and routine antibiotics, was utilized.

Renal function investigations. In the hypothermia experiments, the bypass was divided into 4 stages; (1) a period of bypass without active cooling, varying from a few minutes to half an hour, followed by (2) a period of cooling to about 10° C., often in stages, then (3) a static period without active cooling or warming, and finally (4) a period of active rewarming.

Urine collections were obtained from a catheter tied in one or both ureters. The ureters were exposed through a small flank incision and dissected out retroperitoneally. The tip of the catheter was inserted into the renal pelvis and tied firmly in place. Collections were obtained over accurately timed intervals. They were begun at least 20 minutes after the intravenous infusions had been begun and between 7 and 60 minutes before bypass was started to enable prebypass control estimations to be performed. After the completion of the bypass, urinary function was followed in 8 of the 9 dogs for an additional 10 to 79 minutes to enable postbypass control estimations to be made.

Blood samples were taken every 10 to 15 minutes throughout each experiment, usually at the midpoint of each urine collection period.

Each dog received 2 intravenous infusions throughout the experiment. The one which was given into the forelimb consisted of a 10 per cent solution of dextrose in water, and this was run at a rate to ensure a urinary flow of 1 to 6 ml. per minute prior to bypass. No attempt was made to stabilize the urinary flow. The other infusion, which was given through the needle in the vein in the right hindleg, consisted in each case of 1.5 Gm. of creatinine dissolved in 1 L. of 0.9 normal saline solution. This was run at about 4 ml. per minute via a constant rate drip apparatus. Each dog received a priming dose of 0.5 Gm. of creatinine. Twenty minutes was allowed for equilibration before the urine or blood collections were made.

With the institution of bypass, the serum creatinine level was immediately lowered as the dog's creatinized blood was diluted with the fresh donor blood used to prime the bypass machine. Conversely, as hypothermia proceeded and the urinary excretion of creatinine diminished, the serum level tended to rise. Thus the constant infusion of creatinine was not in itself sufficient to ensure a constant serum level. For this reason blood samples were taken every 10 to 15 minutes for the estimation of serum creatinine.

Each urine and blood sample was analyzed for osmolality, creatinine, sodium, and potassium, and each urine sample for protein content. Urine volumes were measured to the nearest 0.1 ml. Osmolality was determined by means of a Fiske osmometer, accurate to 2 per cent. Creatinine and quantitative urinary protein were measured by the methods described by King and Wootton.[11] Sodium

*Manufactured by Elektrolaboratoriet, Copenhagen, Denmark.

Table I. *General picture of experiments*

Dog No. and weight (Kg.)	*Experiment*	*Bypass details*	*Total duration of bypass (min.)*	*Plasma Hb. (mg. %)*	*Lowest esophageal temperature (C.)*	*Well 24 hr. after bypass*
1, 15	Hypothermic renal function	30 min. cooling, 30 min. off, 30 min. warming	60+ 30 off	-	11	Yes
2, 21	Hypothermic renal function	Normothermia, cooling, static, warming	106	54	9.3	Yes
3, 17	Hypothermic renal function	10 min. normothermia, 10 min. 25° C., 10 min. 10° C., warming	89	48	11	Yes
4, 20	Hypothermic renal function	Same	71	112	10.2	No
5, 17	Hypothermic renal function	Same	86	228	11.4	Yes
6, 20	Normothermic renal function	30 min. normothermia	30	40	-	Yes
7, 20	Hypothermic renal function	10 min. normothermia, 62 min. cooling, 20 min. static, 44 min. warming	136	-	11.7	Sacrificed
8, 17	Hypothermic renal function	14 min. normothermia, 37 min. cooling, 8 min. static, 31 min. warming	90	87	9.2	No
9, 16	Normothermic renal function	44 min. normothermia	44	35	-	Yes

and potassium concentrations were determined by flame photometry. The creatinine clearances, which were calculated for the periods during which each urine sample was collected, were taken to represent glomerular filtration rate. When the appropriate blood sample had not been taken at the midpoint of the urine collection period, the serum creatinine level for this point was calculated by simple proportion. Calculations were made of the percentages of filtered sodium excreted $\frac{U_{Na}\ V}{P_{Na}\ C_{cr}} \times 100$ and filtered water excreted $\frac{U\ V}{C_{cr}} \times 100$.

RESULTS

Table I represents the general outline of the experiments. The accompanying Figs. 1 through 4 show the results of the renal function studies in graphic form.

Normothermic perfusion results. The results obtained in the 2 normothermic dogs were identical and Fig. 1 depicts the events which occurred in Dog 9.

In the period before bypass, there was a fall in urine volume and creatinine clearance, with a rise in the urine osmolality and sodium concentration. This was usually associated with a slight fall in the blood pressure and all these changes can possibly be attributed to the anesthetic and to the fall in cardiac output as a result of operative manipulation of the heart. The reason for the rise in the urinary sodium concentration which occurred in this control period, however, is not clear.

It can be seen that with the institution of normothermic bypass, despite a constant blood pressure, there was a continuation or exaggeration of the prebypass trends, except for the urinary sodium concentration which fell as soon as the bypass was begun.

Calculations show that in this dog the percentage of filtered water excreted fell from 13 to 7 per cent as a result of bypass. The percentage of sodium excreted similarly fell from 5 to 0.2 per cent.

After completion of bypass there was a rapid return of these parameters to normal, except the urinary potassium level, which remained constantly elevated.

Hypothermic perfusion results. Fig. 2 presents the findings in Dog 4, which was

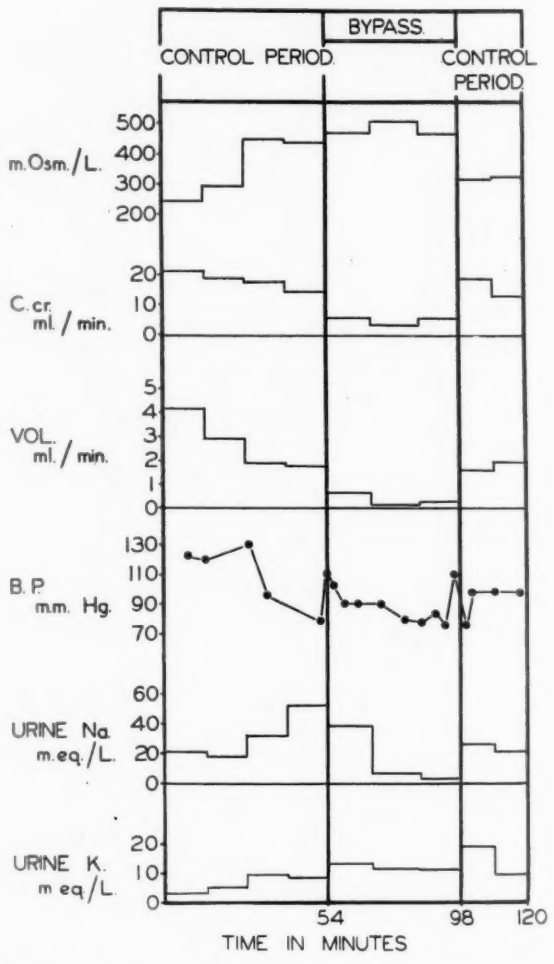

Fig. 1. The events which occurred in the normothermic control dogs, as represented by the typical findings in Dog 9.

selected for discussion because the findings were representative of the whole group of hypothermic dogs.

Changes in blood pressure, creatinine clearance, and urine volume. With the institution of bypass, prior to cooling, a fall occurred in urine volume and creatinine clearance as it did in the normothermic dogs despite the fact that the blood pressure was well maintained at this stage. Immediately after active cooling was instituted, over the course of the first 3 collection periods, there was a rise in creatinine clearance and urine volume to control levels. This occurred in spite of a steady fall in blood pressure.

As cooling and bypass continued, the blood pressure fell progressively in spite of a constant perfusion flow rate, and with this there was now a fall in creatinine clearance and urine volume.

The changes described were rapidly reversed on rewarming. On discontinuation of bypass after rewarming, creatinine clearance remained unchanged and the urine volume increased to levels exceeding the initial control volume.

Urinary sodium, potassium, and percentage of filtered water excreted. With the commencement of active cooling on bypass, the sodium level in the urine rose to approach the serum level. Calculation shows that the percentage of filtered sodium excreted rose from about 1 to 13 per cent at the coldest phase and fell again to about 1 per cent with active rewarming. In addition, the potassium level in the urine fell to approach the serum level.

The percentage of filtered water excreted rose from approximately 6 to 16 per cent and returned to 6 per cent on rewarming.

The urinary sodium and potassium concentrations returned to normal levels with rewarming.

Urine osmolality. The urine osmolality fell to approach serum levels with the commencement of active cooling on bypass. This change was reversed with active rewarming. Immediately after the bypass there was a drop in urine osmolality due to diuresis (increase in urinary volume).

Additional findings in Dog 7. The findings in Dog 7, as compared with those in the other hypothermic dogs, were similar to those discussed and represented in Fig. 2. In addition, however, as can be seen in Fig. 3, 14 minutes after commencement of active cooling a transient and abrupt rise in arterial pressure was apparent. This appeared to be due to an accidental increase in the perfusion flow rate, which was immediately reflected by a marked rise in both urine volume and glomerular filtration rate (creatinine clearance).

Calculations on this dog showed that the percentage of filtered water which was excreted rose from approximately 23 to 72 per cent when the dog was rendered profoundly hypothermic.

Proteinuria. All the dogs except Dog 7 were tested for proteinuria. The concentration of urinary protein during these experiments can be seen in Fig. 4.

In the hypothermic dogs, at 10° C., the urine was protein free, but immediately on commencement of rewarming protein appeared. This reached levels of between 10 and 90 mg. per 100 ml. Only one of the hypothermic dogs tested failed to develop a proteinuria (Dog 3). Dog 1, in which the circulation was stopped during hypothermia and which also developed proteinuria, was not included in Fig. 4. This marked proteinuria did not occur in the 2 normothermic control dogs. In fact, no protein was present in one dog's urine and only a trace was present in that of the other.

DISCUSSION

A diminution in glomerular filtration rate in the presence of active renal tubular function will lead to a rise in urine osmolality and a fall in the percentage of filtered water and sodium excreted. These changes were a constant finding in the normothermic control dogs and in the control bypass period before active cooling (Figs. 1 through 3). During normothermic bypass with high perfusion flow rate, there is thus a drop in glomerular filtration rate in the presence of unimpaired tubular function. The fall in glomerular filtration in the presence of a relatively well-maintained blood pressure is commensurate with the findings of Corday[5] that one of the earliest mechanisms utilized to maintain systemic blood pressure is renal vasoconstriction.

When, however, profound hypothermia is associated with cardiopulmonary bypass, tubular function is impaired (Figs. 2 and 3). The percentage of excreted sodium and water in the urine increased progressively with cooling (in Dog 7, 72 per cent of the filtered water was excreted as urine), indicating the increasing failure of tubular reabsorption, and this was reflected in the decrease of urine osmolality toward serum levels. Additional evidence of tubular failure was a fall in the urinary potassium level.

The progressive drop in blood pressure, despite the constant high perfusion flow rate and shunt of blood from the heart-lung machine into the dog[19, 20, 23] without a rise in venous pressure, is due at least in part to the impairment of the autonomic nervous function which occurs with cooling,[24] resulting in peripheral vasodilation and an increase in the vascular space.

Glomerular filtration rate and urinary volume promptly rose despite a concomitant fall in blood pressure with the institution of active cooling, and is in accord with Segar's[21, 22] findings that hypothermia induces a marked diuresis in the dog. It appears that at least 2 mechanisms contribute to this phenomenon. One is the transitory increase in glomerular filtration rate, which leads to an immediate and marked increase

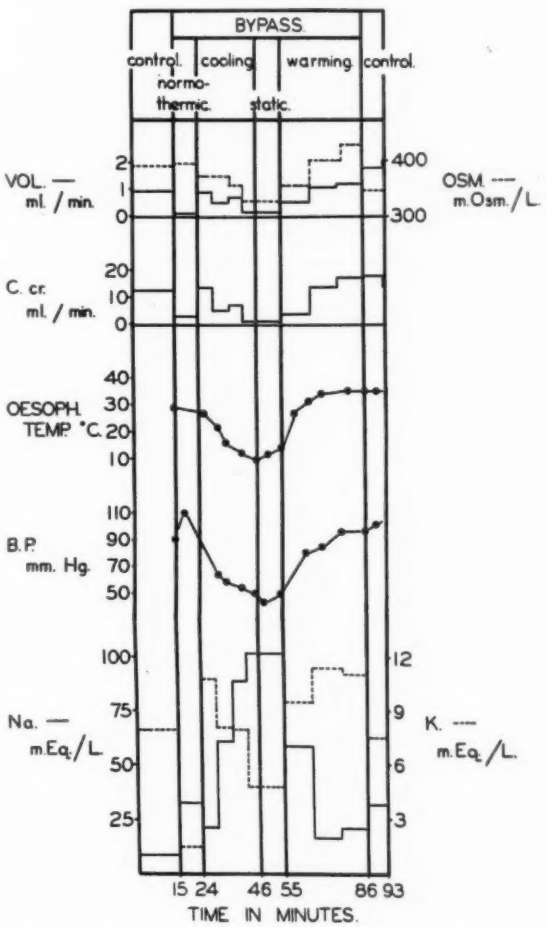

Fig. 2. The events which occurred in the hypothermic dogs, as represented by the typical findings in Dog 4.

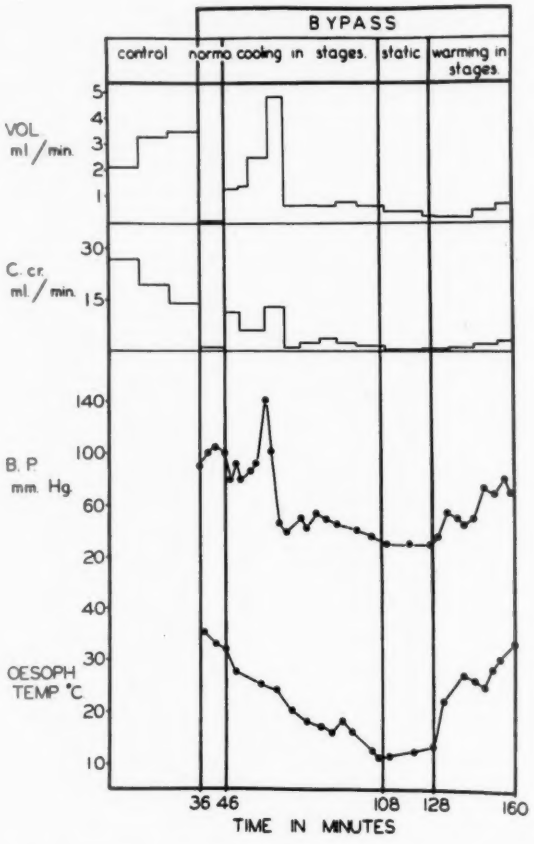

Fig. 3. The findings in hypothermic Dog 7, in which the bypass technique differed from the others in this series.

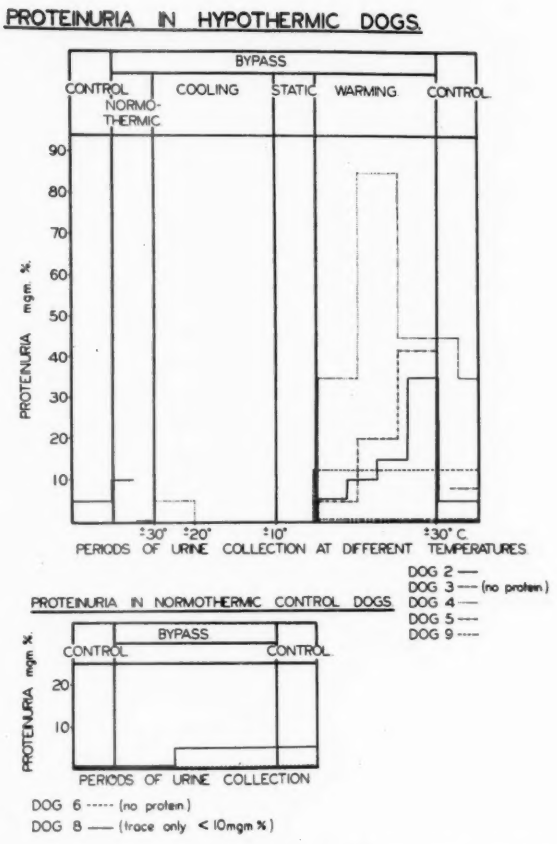

Fig. 4. The results of proteinuria tests which were carried out on all the dogs in this series except Dogs 1 and 7.

in urine volume; the other mechanism is the progressive failure of tubular reabsorption of water. The importance of the latter mechanism in hypothermic diuresis has not hitherto been fully appreciated. In the hypothermia experiments there was a closer relationship between glomerular filtration rate, urinary volume, and blood pressure than was observed during normothermic bypass. This phenomenon was clearly shown (1) by the fall and rise which occurred in glomerular filtration rate and urine volume, associated with fall and rise in blood pressure (Figs. 2 and 3), and (2) the accidental increase in perfusion rate, which occurred in Dog 7 and immediately caused a transitory rise in blood pressure, was associated with an immediate rise in glomerular filtration rate and urine volume (Fig. 3).

An important finding in this study was the immediate reversal of all the changes brought about by profound hypothermia on rewarming. If one uses as indices of tubular function the degree of reabsorption of filtered water, sodium, excretion of potassium, and elaboration of concentrated or dilute urine, one can conclude that tubular functions have returned promptly to control levels on rewarming. In only 1 of the 6 hypothermic dogs in which postbypass function was studied did the glomerular filtration rate not return to prebypass level.

In 5 of the 6 hypothermic dogs in which this test was made, proteinuria developed on rewarming. If proteinuria per se is an indication of renal damage, it must be concluded that hypothermia, or the rapid rewarming of the cold organ, can damage the canine kidney in the presence of a high perfusion flow rate. We believe, however, that proteinuria per se is not necessarily an indication of renal damage (as in athletes). It thus seems that

the use of profound hypothermia, which is such a useful adjunct in certain branches of modern surgery, is justified, as the extreme changes in renal function which occur during its application are promptly reversed on rewarming.

The effects of cold on the kidney on both dog and in man, usually induced by surface cooling, have been extensively studied.[1, 3, 4, 8-10, 14-18] Even at these temperature levels Segar[21, 22] was able to detect some disturbance of renal tubular function.

In this study, evidence that profound hypothermia affects the tubular transport mechanism was obtained. Further study of this aspect is in progress and will be the subject of another report.

CONCLUSIONS AND SUMMARY

Seven dogs have been used to observe the variations in renal function which occur during and just after profound hypothermia is induced and maintained by means of an efficient heat exchanger in the arterial line of the bubble oxygenator system. In addition, 2 dogs were subjected to high flow rate normothermic perfusions to act as controls.

Six important points were elicited from these experiments.

1. The changes in renal function which occur during bypass without hypothermia are those associated with a fall in glomerular filtration rate in the presence of normally functioning renal tubules. This fall is apparently out of all proportion to the relatively well-maintained blood pressure. Subsequent to bypass, when the glomerular filtration rate returns to control values, these changes are reversed.

2. The changes in renal function which occur during bypass with profound hypothermia contrast sharply with those which occur with normothermic bypass. Tubular function (as evidenced by the changes in urinary sodium and potassium concentrations, urinary osmolality, and the increase of percentage excretion of filtered water and sodium) becomes progressively impaired, a progressive drop in blood pressure occurs despite the maintenance of a constant high perfusion flow rate, initiation of hypothermia induces a transitory increase of glomerular filtration rate and urine volume, and a more obvious relationship between glomerular filtration rate, urine volume, and blood pressure occurs.

3. Rewarming after profound hypothermia leads to a prompt reversal of the above changes.

4. This reversal is maintained in the immediate postbypass period.

5. During the induction and maintenance of profound hypothermia there is no proteinuria. With rewarming, proteinuria immediately occurs. The significance of this is not certain.

6. In the dog, the prompt reversal of the other abnormal renal functions on rewarming lends support to the continued use of profound hypothermia.

We wish to thank Prof. J. H. Louw of the Department of Surgery, University of Cape Town, for his continued support of our research work and the technical staff, Messrs. C. C. Goosen and C. J. Lockett, and Mrs. V. M. Connell, for their unflagging assistance. Thanks go also to Mrs. P. Kottler for graphs and Mr. G. McManus for photography. Finally, we are indebted to the Council for Scientific and Industrial Research and to the Dr. C. L. Herman Research fund of the University of Cape Town for the financial support of this project.

REFERENCES

1. Andersen, M., and Nielsen, K. C.: Studies on the renal function under experimental hypothermy in rabbits, Acta med. scandinav. **151:** 191, 1955.
2. Barnard, C. N., McKenzie, M. B., and De Villiers, D. R.: Preparation and assembly of the stainless steel sponge debubbler for use in the helix reservoir bubble oxygenator, Thorax **15:** 268, 1960.
3. Bergstrand, A., and Sterky, G.: Renal function in hypothermia, Acta Physiol. Scandinav. **31:** 13, 1954.
4. Blatters, C. M., and Horvath, S. M.: Renal, cardiovascular and respiratory response and their interrelations during hypothermia, Am. J. Physiol. **192:** 357, 1958.
5. Corday, E., and Williams, J. H., Jr.: Effect of shock and of vasopressor drugs on the regional circulation of the brain, heart, kidney and liver, Am. J. Med. **29:** 228, 1960.

6. DeWall, R. A., Warden, H. E., Read, R. C., Gott, V. L., Ziegler, N., Varco, R. L., and Lillehei, C. W.: A simple, expendable, artificial oxygenator for open-heart surgery, S. Clin. North America **36:** 1025, 1956.
7. DeWall, R. A., Warden, H. E., Varco, R. L., and Lillehei, C. W.: The helix reservoir pump oxygenator, Surg. Gynec. & Obst. **104:** 699, 1957.
8. Hong, S. K.: Renal function during hypothermia and hibernation, Am. J. Physiol. **188:** 137, 1957.
9. Hong, S. K., and Boylan, J. W.: Renal concentrating operation in hypothermic dogs, Am. J. Physiol. **196:** 1150, 1959.
10. Kanter, G. S.: Renal clearance of glucose in hypothermic dogs, Am. J. Physiol. **196:** 866, 1959.
11. King, E. J., and Wootton, I. D. P.: Microanalysis in medical biochemistry, London, 1956, J. & A. Churchill Ltd.
12. McKenzie, M. B., and Barnard, C. N.: Experimental studies in extracorporeal circulation using the helix reservoir bubble oxygenator, South African **M. J. 32:** 1145, 1958.
13. McKenzie, M. B., and Barnard, C. N.: A note on priming the DeWall oxygenator, South African **M. J. 34:** 108, 1960.
14. Miles, B. E., and Chirchill-Davidson, H. C.: The effect of hypothermia on the renal circulation of the dog, Anesthesiology **16:** 230, 1955.
15. Morales, P., Carbery, W., Morello, A., and Morales, G.: Alteration in renal function during hypothermia in man, Ann. Surg. **145:** 488, 1957.
16. Moyer, J. H.: The effect of hypothermia on renal function and renal damage from ischaemia, Ann. New York Acad. Sc. **80:** 424, 1959.
17. Moyer, J. H., Morris, G., and De Bakey, M. E.: Hypothermia. I. Effect on renal hemodynamics and on excretion of water and electrolytes in dog and man, Ann. Surg. **145:** 26, 1957.
18. Page, L. B.: Effects of hypothermia on renal function, Am. J. Physiol. **181:** 171, 1955.
19. Robard, S., Saiki, H., Malin, A., and Young, C.: Significance of changes in plasma and extracellular volumes in induced hypothermia and hyperthermia, Am. J. Physiol. **167:** 485, 1951.
20. Sanger, P. W., Robicsek, F., Taylor, F. H., Rees, T. T., and Stam, R. E.: Vasomotor regulation during extracorporeal circulation and open-heart surgery, J. Thoracic Surg. **40:** 355, 1960.
21. Segar, W. E.: Effect of hypothermia on tubular transport mechanisms, Am. J. Physiol. **195:** 91, 1958.
22. Segar, W. E., Riley, P. A., Jr., and Barila, T. G.: Urinary composition during hypothermia, Am. J. Physiol. **185:** 528, 1956.
23. Simpson, J. A., Gibson, P., and Bloomfield, D. A.: Profound hypothermia in cardiac surgery, M. J. Australia **47:** 647, 1960.
24. Terblanche, J.: Unpublished data, 1961.
25. Terblanche, J., and Barnard, C. N.: Profound hypothermia using extracorporeal circulation without an artificial oxygenator, South African M. J. **34:** 1003, 1960.

Retrograde transductal internal drainage of pancreatic pseudocyst

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Recently, we had occasion to treat a patient with a long history of chronic alcoholic pancreatitis complicated by development of a pancreatic pseudocyst associated with obstructive jaundice. It was elected to manage both the chronic pancreatitis and the pseudocyst by internal caudal drainage of the pancreatic duct. To our knowledge, this type of approach had not been described previously. Caudal pancreatic drainage, in our experience, has proved to be a satisfactory method of decompressing the pancreatic duct in patients with chronic pancreatitis. The purpose of this report is to indicate the feasibility of simultaneous drainage of a pseudocyst via this route.

CASE REPORT

A 43-year-old man was admitted for the first time to the Surgical Service, Veterans Administration Hospital. During the preceding month he had experienced severe epigastric pain, diarrhea, progressively deepening jaundice, and a 30-pound weight loss. Of singular importance in this patient's history was his readily admitted heavy alcoholic intake which dated back to adolescence. The patient had suffered frequent episodes of epigastric pain accompanied by nausea and vomiting over the past 17 years. During the past 8 years these episodes had become more frequent and required 10 admissions to various institutions with diagnoses of acute and chronic pancreatitis. He had obtained moderate relief of symptoms from antispasmodics and dietary measures. The stools gradually became loose and foamy. Five years prior to this admission pancreatic calcification had been recognized. Two years later, a liver biopsy demonstrated portal cirrhosis. One year prior to admission diabetes became evident.

Upon examination jaundice was obvious. The liver was enlarged and the gall bladder was palpable below the liver edge. In the epigastrium a separate smooth, tense mass was palpable. This mass was also readily visible and had all the characteristics of a pancreatic pseudocyst. An upper gastrointestinal series confirmed this impression and also suggested that the cyst was expanding behind the antrum and first portion of the duodenum (Fig. 1, *A*). The significant laboratory findings were an elevated bilirubin level (11.0 mg. per 100 ml.) and hyperglycemia. Results of liver function tests suggested obstructive jaundice. Serum amylase was normal.

The patient underwent abdominal exploration through a bilateral subcostal incision on Oct. 5, 1960. Our preoperative impression was confirmed by the finding of a 15 by 15 by 17 cm. cystic mass overlying the head of the pancreas and bulging behind the antrum and the first portion of the duodenum into the hepatoduodenal ligament. The gall bladder was enlarged, tense, and edematous. A cholangiogram (Fig. 2, *A*) showed obstruction of the distal portion of the common bile duct by extrinsic compression. The tail and head of the pancreas exposed through the gastrocolic ligament had the characteristic diffuse, gritty induration of chronic pancreatitis. The major duct could not be palpated on the surface of the gland. The caudal portion of the pancreas was mobilized and its tip (0.5 cm.) was amputated after removal of the spleen in order to expose the lumen of the major pancreatic duct. A moderate amount of turbid fluid came from the duct as it was opened. This flow could be increased slightly by compression of the cyst. The duct was opened longitudinally up to the level of the mesenteric vessels in the manner described by Puestow.[3] The cephalic portion of the duct was explored and several stones were removed from the lumen. Considerable narrowing of the distal pancreatic duct

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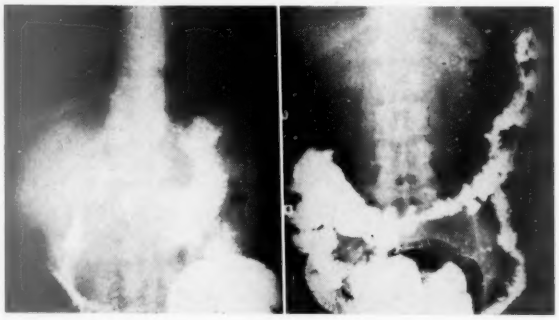
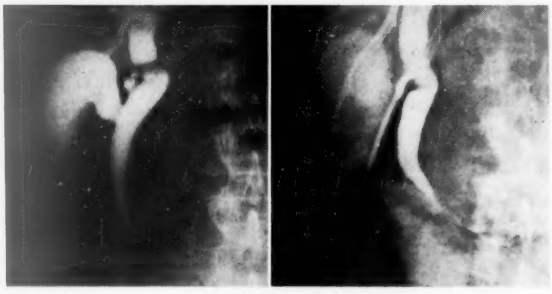


A *B*

Fig. 1. *A,* Preoperative upper gastrointestinal series demonstrates extrinsic compression of antrum and proximal duodenum by posterior mass. *B,* Preoperative barium enema shows downward displacement of transverse colon. Extensive pancreatic calcification is obvious.



A *B*

Fig. 2. *A,* Operative cholangiogram taken prior to evacuation of cyst contents demonstrates complete bile duct obstruction due to extrinsic compression of distal bile duct. *B,* Operative cholangiogram taken after evacuation of cyst contents. Note passage of contrast medium into duodenum and absence of cicatricial scarring of the duct.

was obvious upon probing after removal of the stones. A fine-tipped curved clamp was then guided blindly into one of the anterior ramifications of the cephalic portion of the pancreatic duct and with moderate perssure was introduced into the cystic cavity (Fig. 3). There was an immediate gush of dark fluid (1,000 ml.) from the duct as the cyst emptied (Fig. 4). The opening between the cyst and the major pancreatic duct was then enlarged by spreading the jaws of the clamp several times. The tail of the pancreas was anastomosed to a Roux Y jejunal loop (Fig. 3). Another operative cholangiogram taken after drainage of the cyst had been completed (Fig. 2, *B*) showed prompt passage of the dye into the duodenum. In view of the absence of cicatricial scarring of the distal portion of the duct, a cholecystectomy alone was performed.

The patient's postoperative course was uneventful. He was discharged on the thirty-fifth postoperative day after an additional operation for an old traumatic defect of the upper lip. The patient was gaining weight and for the first time in many years was free from abdominal pain and was passing formed, nongreasy stools. He has been seen regularly since and continues to do well.

DISCUSSION

The principle of internal drainage of pseudocystic lesions of the pancreas is well accepted. Excellent and up-to-date reviews of this problem have been published.[4] There are several methods of internal drainage, but little objective evidence for giving preference to any particular one. We have always preferred to drain pancreatic pseudocysts via a retrocolic Roux Y jejunal loop anastomosed to the cyst in as dependent a position as possible, in order to ensure efficient gravity drainage of the cystic cavity at all times. In our opinion, this is the ideal operation for a large pseudocyst presenting between the stomach and transverse colon behind the gastrocolic ligament. However, there are pseudocysts such as the one in our patient which develop behind the antrum and first portion of the duodenum, compressing these and adjacent structures to the point of pyloric obstruction or obstructive jaundice. Their location may render a cystojejunostomy somewhat impractical. Cystoduodenostomy or cystogastrostomy has been performed for lesions in this location with apparently good results.[4] However, both cystoduodenostomy or cystogastrostomy have the theoretical disadvantage of transforming the pancreatic pseudocyst into a diverticulum of the gastrointestinal tract. Moreover, these operations as well as the other methods of internal drainage do not correct the underlying pancreatic pathologic process. This is unimportant when a pancreatic pseudocyst develops after a first attack of acute pancreatitis or after pancreatic trauma. However, if the patient already has recurrent acute pancreatitis or well-established chronic relapsing pancreatitis, surgical treatment of the underlying pancreatic disease as well as of the pseudocyst should

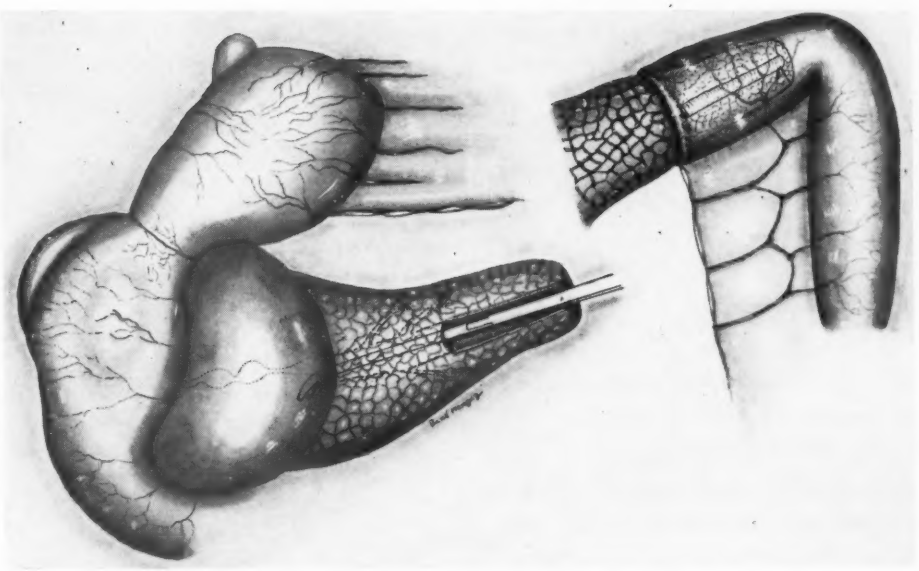


Fig. 3. Schematic illustration of operative technique.

be an important consideration. In this regard Doubilet[1] has described a technique of draining pancreatic pseudocysts through the sphincter of Oddi after sphincterotomy via a small plastic tube introduced into the cyst through the pancreatic duct and brought out through the common bile duct with a T tube. Although this method seems appealing, we have always experienced some difficulty in exploring the pancreatic duct through the sphincter of Oddi. On the other hand, we find exploration of the pancreatic duct through its distal end to be technically simple. Furthermore, in our experience as well as that of others,[3] pancreatic ductal obstruction in chronic pancreatitis is a diffuse, stenosing process involving long segments of the cephalic portion of the duct proximal to the sphincter of Oddi. Under these conditions, sphincterotomy is an illogical procedure and cannot be expected to achieve its proposed goal of enhancing drainage of pancreatic secretions into the lumen of the intestine.

Our results with caudal pancreatic drainage in treating chronic pancreatitis have been sufficiently good to warrant use of the principle of caudal drainage to manage both chronic pancreatitis and associated pseudocyst. The purpose of this report is to indicate the feasibility, the technical simplicity, and the satisfactory result of this approach in at least 1 case. The procedure described is certainly not applicable to all pseudocysts. In our opinion, cystic lesions located around the head of the pancreas or occurring in patients with a history either of chronic pancreatitis or suggesting the development of chronic pancreatitis would benefit by this combined technique.

To prevent diabetes or to avoid aggravating diabetes if already present, it is important to remove as little pancreatic tissue as possible. We usually amputate a very short segment (0.5 cm.) of the tip to expose the

Fig. 4. Photograph taken at the moment the clamp was introduced into the cyst on the left. Stomach is retracted above. Clamp lies in the opened duct. Note cyst fluid gushing out of the duct.

ductal lumen. Actually, the tail of the pancreas can be anastomosed to an intestinal loop without prior mobilization.[2] Our only reason for preferring the former method is that we believe that pancreaticojejunostomy is easier and more secure when the body and tail of the pancreas are invaginated into the jejunum.

SUMMARY

A patient with long-standing pancreatitis complicated by recent development of a large pancreatic pseudocyst was treated successfully by combined retrograde decompression of the pancreatic duct and the pseudocyst via a caudal pancreaticojejunostomy.

The patient was seen in July, 1961. Clinical and radiologic data showed complete cure of the cyst. Symptoms of chronic pancreatitis were considerably improved.

REFERENCES

1. Doubilet, H., and Mulholland, J. H.: Pancreatic cysts, Surg. Gynec. & Obst. **96:** 683, 1953.
2. Partington, P. F., and Rochelle, R. E. L.: Modified Puestow procedure for retrograde drainage of the pancreatic duct, Ann. Surg. **152:** 1037, 1960.
3. Puestow, C. B., and Gillesby, W. J.: Retrograde surgical drainage of pancreas for chronic relapsing pancreatitis, A. M. A. Arch. Surg. **76:** 898, 1958.
4. Warren, W. D., Marsh, W. H., and Sandusky, W. R.: An appraisal of surgical procedures for pancreatic pseudocyst, Ann. Surg. **147:** 903, 1958.

An evaluation of actinomycin D and mitomycin C in patients with advanced cancer

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During the past several years, various antibiotic substances have been tested in the screening program of the Cancer Chemotherapy National Service Center. Those that have shown activity against the animal tumor screens have then been tested against human tumors in an attempt to find an active anticancer agent and also to determine a spectrum of activity for various groups of drugs. At the Minneapolis Veterans Administration Hospital and the University of Minnesota Hospitals, 2 of these substances, antinomycin D and mitomycin C have undergone clinical study.

Actinomycin D is obtained from cultures of *Streptomyces parvullus*. The preparations now available are probably mixtures, with the relative amounts of the different actinomycins varying with each preparation. The mode of action of actinomycin D is not understood. In mice, it produces a decrease in the spleen weight, atrophy of the thymus and lymph nodes, and ulceration of the gastrointestinal tract.[1] It has been inactive when given orally. A very thorough review of the chemical and biological properties of this drug has been published by Moore.[4]

Mitomycin C is obtained from the broth of *Streptomyces casepitosus*. This drug causes a reduction in the size of the thymus and spleen, hemorrhage into the mesenteric lymph nodes, and a bloody diarrhea in mice.[5] It has a pronounced effect upon the bone marrow of dogs. The inhibition of *E. coli* that is caused by this drug may be reversed by guanine or xanthine.[6] In extensive preclinical trials, mitomycin C was found to have one of the widest spectrums of action against animal tumors of any substance screened.

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METHODS

The patients treated with these drugs all had a malignancy that was incurable by presently known methods of therapy. The diagnosis in each case was proved by biopsy taken at operation or at the time of autopsy. All of the patients were hospitalized during the entire course of treatment. White blood cell and platelet counts were made in all cases every other day and, in addition, for the first few patients given each drug, liver and kidney function studies were carried out before and at the end of therapy.

Actinomycin D was dissolved in 25 per cent ethanol. The solution given intravenously contained 0.25 mg. of the drug per milliliter. Mitomycin C was diluted to 0.5 mg. per milliliter in 0.01 M phosphate buffer and given intravenously. It was used immediately after dissolving because of evidence that the drug loses its potency in solution.[10]

RESULTS

Twenty-one patients were treated with actinomycin D. The results of this therapy

Table I. *Actinomycin D*

Patient	*Diagnosis*	*Performance status[3] (%)*	*Total dose (μg/Kg.)*	*Lowest WBC*	*Day of lowest WBC*	*Other evidence of toxicity*	*Objective improvement*	*Subjective improvement*
1 A. K.	Adenocarcinoma of colon	40	75	No depression	—	Severe ulceration of lips and tongue	None	None
2 A. G.	Adenocarcinoma of colon	50	75	1,550	15	Generalized erythema, ulceration of lips and tongue	None	None
3 N. D.	Adenocarcinoma of colon	50	65	No depression	—	Ulceration of lips, nausea and vomiting	None	None
4 T. T.	Adenocarcinoma of rectum	40	75	3,770	15	Fever, generalized erythema	None	None
5 C. V.	Adenocarcinoma of colon	30	65	No depression	—	Death on day 15 unrelated to drug	None	None
6 L. B.	Adenocarcinoma of rectum	60	65	No depression	—	None	None	None
7 A. M.	Squamous-cell carcinoma of tongue	40	65	No depression	—	None	None	None
8 L. D.	Squamous-cell carcinoma of tongue	50	75	No depression	—	Generalized maculopapular rash, severe oral ulceration, confusion	None	None
9 P. C.	Squamous-cell carcinoma of lip	80	75	No depression	—	None	None	None
10 P. A.	Squamous-cell carcinoma of piriform sinus	70	75	3,450	15	None	None	None
11 L. F.	Squamous-cell carcinoma of abdominal scar	30	65	No depression	—	Death on day 15 not related to drug	None	None
12 G. R.	Basal-cell carcinoma of face	30	65	No depression	—	Died on day 5	None	None
13 R. B.	Adenocarcinoma of stomach	60	65	No depression	—	None	None	None
14 A. H.	Adenocarcinoma of pancreas	40	75	No depression	—	Oral ulceration, ulcer of arytenoids, grand-mal seizures	None	None
15 K. T.	Wilms' tumor	40	65	No depression	—	None	None	None
16 W. N.	Wilms' tumor	50	70	No depression	—	None	None	None
17 A. H.	Adenocarcinoma of breast	80	75	No depression	—	Total alopecia, severe ulceration of mouth	None	None
18 L. R.	Synovioma of arm	70	75	No depression	—	Oral ulceration	None	None
19 S. L.	Malignant melanoma	30	65	No depression	—	None	None	None
20 A. C.	Ewing's sarcoma	40	65	No depression	—	None	None	None
21 J. M.	Hodgkin's disease	50	75	No depression	—	None	Loss of fever	Weight gain

are summarized in Table I. Two dosage schedules were employed, the first was 75 μg per kilogram given in divided doses over 5 days and the other was 65 μg per kilogram given in the same manner. The higher dosage level resulted in the development of toxicity in a large percentage of the patients, while at the 65 μg level, toxicity was quite infrequent. Toxicity was manifested most commonly by ulcerations of the lips, tongue, and buccal mucous membrane. Mild nausea was also fairly common, but in no case was it severe. A maculopapular skin eruption occurred in 4 patients. From Table I it is apparent that few patients developed a bone marrow depression and in the cases in which it did occur, it was quite mild. One woman (A. H.) developed a marked alopecia; however, her hair returned during the ensuing 6 months. Three patients died shortly after completing the course of therapy; none of these deaths seemed to be directly related to the drug. In only 1 case did the drug seem to affect favorably the course of the patient's disease; this was in the patient with Hodgkin's disease (J. M.) who developed a remission which lasted for 3 months.

In Table II are listed the patients treated with mitomycin C. The dosage schedule used was 50 μg per kilogram per day for 6 days, and then 50 μg per kilogram every other day until toxicity occurred. In contrast to actinomycin D, the only important manifestation of toxicity to mitomycin C was bone marrow depression. On this dosage schedule, a mild depression of the white blood cell count was quite common, yet severe depression did not occur. Of the 3 deaths which occurred while the effect of the drug was still present, none was thought to be directly related to the therapy. Only 2 patients showed any objective evidence of tumor regression after treatment with mitomycin.

CASE REPORTS

Case 15. A. F. was a 65-year-old man admitted with a 2-month history of weight loss and difficulty in swallowing. An esophagram at that time showed a filling defect in the middle third of the esophagus. The patient refused a thoracotomy and was discharged. Four months later the patient was again admitted with nodular densities in the left lower and right upper lobe of the lung. A biopsy during esophagoscopy was not contributory. The man was discharged. When he was readmitted for the third time 4 months later, he was hoarse and had weakness and numbness of the right hand and the right side of the face. Shortly afterward he developed a complete right hemiplegia with aphasia. Mitomycin C, 50 μg per kilogram, was started and at the end of 2 weeks the aphasia had disappeared and the right hemiplegia had improved. This improvement lasted approximately 1 month after which the patient's condition began to deteriorate. A second course of mitomycin C was ineffective and the patient died 3 months after the first course of mitomycin had been started. An autopsy showed a squamous-cell carcinoma of the esophagus.

Case 20. R. E. was a 60-year-old man admitted with a 3-month history of anorexia, weight loss, and epigastric pain. On physical examination, he was found to have a 10 by 10 cm. hard mass in the epigastrium. He underwent exploratory operation and a large carcinoma of the pancreas was found that surrounded the superior mesenteric vessels and involved lymph nodes in the porta hepatis and the mesentery of the small bowel. No resection was performed. The patient was given a total of 116 mg. of mitomycin C beginning 10 days after laparotomy. At the end of 1 month, the epigastric mass had completely disappeared and the patient was essentially free of pain. One month later, however, the pain returned and the liver became progressively larger. His condition deteriorated and he died 3 months after the mitomycin had been started.

DISCUSSION

Reports of clinical trials of actinomycin D in a wide spectrum of human tumors in both children and adults have been published, but only in Wilms' tumors in children have fairly frequent responses been seen. Farber[2] has reported a 2 to 50 month survival in 35 per cent of the patients with this tumor and Tan and associates[8] found an objective response in 4 of 15 patients with Wilms' tumor. Occasional remissions have been seen in children with neuroblastoma or rhabdomyosarcoma.[7, 8] In adult patients, objective remissions of malignant disease have been few. Of the 20 patients with either a carcinoma or sarcoma in our series, none showed any subjective or objective improvement. It seems that this drug should be considered to have a low therapeutic potential in human tumors.

Table II. *Mitomycin C*

Patient	*Diagnosis*	*Performance status*[3] (%)	*Total dose (mg.)*	*Lowest WBC*	*Day of lowest WBC*	*Other evidence of toxicity*	*Subjective improvement*	*Objective improvement*
1 R. B.	Carcinoma of prostate	40	30.4	3,900	17	None	Disappearance of back pain	None
2 C. H.	Carcinoma of prostate	40	41.0	No depression	—	None	Mild pain relief	None
3 H. H.	Carcinoma of prostate	30	25.8	2,750	7	None	Pain relief, decrease in nausea	None
4 O. S.	Carcinoma of prostate	40	18.9	3,900	16	None	Pain relief	None
5 W. B.	Squamous cell carcinoma of renal pelvis	40	29.0	No depression	—	None	None	None
6 S. S.	Adenocarcinoma of rectum	60	23.2	4,000	7	None	—	None
7 B. L.	Adenocarcinoma of colon	30	28.0	3,500	15	None	None	None
8 G. H.	Squamous-cell carcinoma of esophagus	30	10.0		Died on day 4 of therapy		None	None
9 J. C.	Squamous-cell carcinoma of mouth	30	34.8	2,450	29 Died on day 32	None	None	None
10 C. T.	Squamous-cell carcinoma of tongue	40	28.1	No depression	—	None	None	None
11 C. J.	Squamous-cell carcinoma of tonsil	40	24.8	2,000	24	None	None	None
12 L. Q.	Squamous-cell carcinoma of floor of mouth	60	43.5	3,350	37	None	None	None
13 F. J.	Adenocarcinoma (primary unknown)	50	30.0	No depression	—	None	None	None
14 A. J.	Undifferentiated carcinoma (primary unknown)	70	26.4	No depression	—	None	None	None
15 A. F.	Squamous-cell carcinoma of esophagus	30	35.7	4,250	14	None	—	Disappearance of aphasia and hemiplegia
16 J. C.	Carcinoma of thyroid	50	14.4	3,850	12	None	None	None
17 W. T.	Glioblastoma multiforme	30	25.8	No depression	—	None	None	None
18 E. P.	Chondrosarcoma of hip	80	63.9	3,150	38	None	None	None
19 G. M.	Adenocarcinoma of pancreas	40	52.5	No depression	—	None	None	None
20 R. E.	Adenocarcinoma of pancreas	40	116	2,400	30	None	Pain relief	Disappearance of abdominal mass
21 R. W. E.	Adenocarcinoma of pancreas	40	20.1	3,400	15	None	None	None
22 N. B.	Adenocarcinoma of stomach	40	56.4	1,400	42	Dead on day 44	None	None

Mitomycin C was first introduced into clinical trial in Japan. Reports from that country indicated that a high degree of antitumor activity could be obtained in man, with an acceptable degree of toxicity. Tasaka and colleagues[9] reported objective improvement in 12 of 36 cases. Yorimae and his group[11] found improvement in carcinoma both of the stomach and of the colon. In contrast to these results, reports from this country have stated the drug to be extremely toxic and of little benefit in the treatment of advanced cancer. Severe bone marrow depression has occurred with doses as low as 0.3 mg. per kilogram. With the dosage schedule reported here, severe leukopenia was not found to be a problem. However, of the 22 patients treated with this drug only 2 showed even a short-term objective response, although admittedly these 2 had tumors which are characteristically refractory to chemotherapy. It does not seem that this drug will be an important addition to our therapeutic measures for human cancer.

SUMMARY

Twenty-one patients were treated with actinomycin D and 22 with mitomycin C. The principal toxic effects of actinomycin D were ulceration of the mouth and pharynx, nausea, and dermatitis, while the main toxic effect of mitomycin C was bone marrow depression. One patient with Hodgkin's disease improved with actinomycin D. Short improvement was found in a case of carcinoma of the pancreas and carcinoma of the esophagus with mitomycin C. Neither of these drugs is considered to have great value in the treatment of human malignancy.

REFERENCES

1. DiPaolo, J. A., Moore, G. E., and Niedbala, T. R.: Experimental studies with actinomycin D, Cancer Res. **17:** 1127, 1957.
2. Farber, S.: Actinomycin D, M. News **6:** 11, 1960.
3. Karnofsky, D. A., and Burchenal, H.: The clinical evaluation of chemotherapeutic agents in cancer, Symp. Sect. Microbiol., New York Acad. Med. (1948), No. 2, p. 191, 1949.
4. Moore, G. E., DiPaolo, J. A., and Kondo, T.: The chemotherapeutic effects and complications of actinomycin D in patients with advanced cancer, Cancer **11:** 1204, 1958.
5. Phillips, F. S., Schwartz, H. S., and Sternberg, S. S.: Pharmacology of mitomycin C. I. Toxicity and pathologic effects, Cancer Res. **20:** 1359, 1960.
6. Reilly, H. C., Cappuccino, J. G., and Harrison, D. M.: Studies on mitomycin X, a tumor-inhibiting antibiotic, Proc. Am. A. Cancer Res. **2:** 338, 1958.
7. Shaw, R. K., Moore, E. W., Mueller, P. S., Frei, E., III, and Watkin, D. M.: The effect of actinomycin D on childhood neoplasms, A. M. A. J. Dis. Child. **99:** 628, 1960.
8. Tan, C. C. T., Phillips, R. F., Murphy, M. L., and Burchenal, J. H.: Clinical studies with actinomycin D, Acta Un. Int. Cancer **16:** 927, 1960.
9. Tasaka, S., Mashimo, H., Kusoda, Y., Harada, T., Shimizu, K., Okochi, K., Hatakiyama, M., and Kunii, O.: Basic and clinical studies on mitomycin, Gann No Rinsho **5:** 57, 1959.
10. Wakaki, D., Marumo, H., Tomioka, K., Shimizu, G., Kato, E., Kamoda, H., Kudo, S., and Fujimoto, Y.: Isolation of new fractions of antitumor mitomycins, Antibiot. & Chemother. **8:** 228, 1958.
11. Yorimae, H., Knido, T., Ikada, Y., and Sakakibara, N.: Clinical experience with mitomycin C administration, Shinyaku to Rinsho **8:** 53, 1959.

Carcinosarcoma of the lung

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Carcinosarcoma is one of the rarest types of malignant neoplasm to be found in man. It is encountered most frequently in the uterus. It has been reported as occurring with decreasing frequency in the hypopharynx, the esophagus, and the lung. Bergmann and associates,[1] in 1951, reported 2 cases of carcinosarcoma of the lung from the Barnes Hospital of St. Louis and reviewed in detail 7 cases[5, 6, 8, 12, 15, 16, 18] recorded in the literature prior to 1951. The earliest case reviewed by them was reported in 1914 by Saltykow.[15] The first case report of pulmonary carcinosarcoma generally is attributed to Kika[9] in 1908. However, no information is available concerning this case. All but one of these cases reviewed by Bergmann and his associates were autopsy cases and represented the terminal picture of this condition. They reviewed 3 additional cases[3, 11, 14] and classified the lesions as "collision tumors" to differentiate them from true carcinosarcoma. Since 1951, 4 cases of carcinosarcoma of the lung have been recorded in the literature.[4, 13, 17] A few additional lesions have been labeled carcinosarcoma of the lung. A review of these reports has failed to establish clearly their identity as carcinosarcomas.[10]

The 2 cases reported by Bergmann and his associates are the first recorded instances of successful pulmonary resection for carcinosarcoma of the lung. Both patients were operated upon by Dr. Evarts Graham, and pneumonectomy was carried out in both. The first case reported by Bergmann and his associates had been cited in an earlier publication by Graham and Womack[7] concerning bronchial adenomas. At that time the tumor had been diagnosed as a mixed bronchogenic carcinoma and sarcoma.

The purpose of this paper is to report a case in which lobectomy was performed successfully for endobronchial carcinosarcoma of the lung and to review in some detail the published experience in 7 clinical cases of carcinosarcoma of the lung.

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CASE REPORT

The patient, a 64-year-old white male college professor, was admitted to the Ball Memorial Hospital on March 26, 1960, because of pain in the right side of the chest of 3 weeks' duration. Two days after the onset of the chest pain the patient had been involved in a minor automobile accident and received some exposure to cold and snow. Shortly thereafter, he noticed the onset of coughing and hemoptysis. A roentgenogram of the chest showed evidence of right lower lobe infiltration (Fig. 1). He was treated for 18 days with Achromycin and bed rest. When a second chest roentgenogram showed no evidence of improvement after 18 days of treatment, he was admitted to the hospital for further study. There had been no weight loss.

His past history was essentially negative. He had suffered from psoriasis for many years. Two small skin cancers had been removed in 1959 and had not recurred. He did not drink and had never smoked. His mother was living at 86 years of age and his father had died at 59 years of a heart attack. There was no known family history of malignancy.

The positive findings on physical examination were limited to an expiratory friction rub anteriorly at the base of the right lung. The patient's weight was 166 pounds. His blood pressure was 114/80 mm. Hg. Results of a urine examination on admission to the hospital were within normal limits. The red blood cell count was 4.5 million and the hemoglobin was 14.5 Gm. The white blood

cell count was 4,700 with a normal differential. The electrocardiogram was within normal limits. The prothrombin time, the platelet count, and the bleeding and clotting times were normal. The blood urea nitrogen was 13. Tuberculin and histoplasmin skin tests were negative.

Bronchoscopic examination was carried out on March 28 under topical anesthesia. An inflammatory reaction was encountered in the right bronchus intermedius. An edematous-appearing tumor mass was found in the lumen of this bronchus and 2 biopsy specimens were taken. Bronchial washings from this area then were obtained. A catheter was left in the right bronchus and bronchograms were made. Culture of the bronchial washings showed *Staphylococcus aureus*. Repeated cytologic studies on the bronchial washings and on sputum samples thereafter were negative. Evidence only of diffuse submucosal chronic inflammation was found on microscopic examination of the biopsy material. The bronchograms showed bronchiectasis of the basal segments of the right lower lobe (Fig. 2). The bronchus intermedius did not fill well and there was a suggestion of an intraluminal mass. Considerable difficulty was encountered in attempting to fill the right lower lobe segments.

The patient was taken to the operating room on April 1, and the right thoracic cavity was entered through the bed of the resected sixth rib. A mass was encountered in the right lower lobe with evidence of considerable inflammatory change throughout the lobe. Frozen section examination of an adjacent lymph node showed only inflammatory hyperplasia. The artery and vein to the right lower lobe were dissected free and ligated with considerable difficulty due to extensive inflammatory reaction in these areas. An abscess was encountered at the emergence of the inferior pulmonary vein from the pericardial sac. This abscess was opened and evacuated. Because of the abscess and the marked inflammatory reaction about it, it was necessary to open the pericardiac sac and to ligate and divide the inferior pulmonary vein within the sac. The right lower lobe finally was dissected free from all surrounding structures and a bronchus clamp was placed across the lower lobe bronchus immediately distal to the origin of the bronchus to the middle lobe. When the bronchus to the lower lobe had been divided, it was apparent that a portion of an unattached endobronchial tumor had been left behind within the bronchus intermedius. The noncrushing bronchus clamp was momentarily released and a blast of anesthetic gas was delivered through the endotracheal tube by the anesthetist. The residual free endobronchial tumor mass was extruded from the bronchial stump and the bronchus clamp was reapplied. The residual endobronchial tumor mass was cylindrical and measured approximately 3 cm. in length. The excised right lower lobe was opened by the attending pathologists and the tumor was found to be largely a pedunculated endobronchial neoplasm. The diagnosis on frozen section was not clear. The presence of sarcoma was suspected. The tumor did not appear to be a bronchial adenoma as had been thought originally. The bronchial stump was closed with interrupted sutures of fine silk and the thoracotomy incision was closed in layers. A catheter for suction had been left in the right side of the chest and brought out through a stab wound.

Gross pathologic examination of the resected lobe showed the presence of a tumor which was pedunculated with a narrow base and consisted largely of multiple, cylindrical, unattached, finger-like endobronchial extensions both distally and proximally into the various adjacent segments of the bronchial tree (Fig. 3). The tumor arose by a narrow pedicle from the posterior basal segment bronchus. At the site of the origin of the tumor, there was a 3 cm. mass resulting from extension of the tumor into the adjacent lung. Distal to the tumor there was evidence of considerable infection and bronchiectasis. Abscesses of varying size were encountered in several areas.

On microscopic examination, the tumor was found to be a carcinosarcoma. The carcinomatous and sarcomatous portions were intermingled (Fig. 4). The sarcoma portion appeared to be forming osteoid in areas. It was largely a fibrosarcoma. In a few areas there were cells with cross striations

Fig. 1. Roentgenogram of the chest shows increased pulmonary markings in the right cardiophrenic area. These findings were interpreted as suggestive of the presence of an acute or chronic pneumonitis.

Fig. 2. Bronchogram of the right lung demonstrates right lower lobe bronchiectasis. There also appears to be a filling defect in the bronchus *(arrow)*.

which resembled rhabdomyoblasts. The epithelial element was typical of epidermoid carcinoma with good intracellular bridges. In a few areas, small epithelial pearls could be identified. The slides were reviewed by Dr. L. G. Montgomery of the Ball Memorial Hospital, Dr. Edith Parkhill of the Mayo Clinic, Dr. J. B. Hazard of the Cleveland Clinic, Dr. A. A. Liebow of the Grace–New Haven Hospital, and Dr. Frank Vellios of the Indiana University Medical Center. All concurred in the diagnosis of carcinosarcoma of the lung.

The postoperative course was uneventful. Chest suction was discontinued and the tube removed 2 days after operation. The patient received postoperative radiation therapy to the mediastinum. He was given 2,000 r as measured in air through an anterior port and the same amount through a posterior port. He was discharged from the hospital on April 24, 24 days after operation. He has continued to do well since his release from the hospital. When last seen, 19 months after operation, there was no evidence of recurrence of carcinosarcoma, and he was carrying his full work load of college teaching.

DISCUSSION

The microscopic pathologic characteristics of pulmonary carcinosarcoma and the findings in 6 of the 7 recorded autopsy cases have been discussed in detail in the excellent paper by Bergmann and associates.[1] They emphasized that both the sarcomatous and carcinomatous elements must be intermingled in the microscopic picture of the true carcinosarcoma. The only autopsy case recorded since 1951 was published in 1956 by Cavallero.[4] Distant metastases, generally involving both the sarcomatous and carcinomatous elements of the tumor, were found in 6 of the 7 autopsy cases. Only in the case recorded by Ogawa[12] in 1929 was the patient found to be free of metastases at the time of postmortem examination.

My principal concern is to consider in some detail the interesting features of the cases of 7 patients who have been subjected to clinical analysis and, in all but one instance, to thoracotomy. Even from the limited published experience with this unusual pulmonary neoplasm, it can be seen that some interesting clinical patterns are beginning to emerge.

Two rather distinct clinical types of pulmonary carcinosarcoma appear to exist. One type of tumor is peripheral in location and exists as a solid parenchymal mass which may attain considerable size. These tumors tend to invade the chest wall and the adjacent mediastinal and vascular structures. They also tend to be associated with relatively early distant metastasis. Their prognosis appears to be poor. The second type of tumor is quite different. Its location is more central and it occurs as a pedunculated endobronchial growth with rather limited parenchymal extension in the area of its pedunculated origin from the bronchial wall. Regional lymph node involvement and distant metastasis appear to be infrequent. The symptoms are produced by bronchial obstruction with distal atelectasis, bronchiectasis, and suppuration. The prognosis with this type of tumor appears to be surprisingly good. Two of the clinical cases were of the solid peripheral type and 5 were of the pedunculated endobronchial type.

Both of the patients with the peripheral solid type of carcinosarcoma were dead at the time of the case reports. The patient of

Hochberg and his associates[8] was a 55-year-old woman who had had a chronic cough for 10 years. In the 4 months prior to operation she had experienced an exacerbation of symptoms with production of mucopurulent sputum and hemoptysis. Roentgen study of the chest showed a rather large, well-circumscribed mass in the left upper lobe. Bronchoscopic and cytologic studies had not been carried out. At thoracotomy, a large mass in the left upper lobe was found to be attached to the anterior chest wall and to the aortic arch. A left upper lobectomy was performed and the patient died 17 hours after operation.

The patient with a solid peripheral tumor reported upon by Peabody[13] was a 74-year-old man who had experienced symptoms of chest pain and hemoptysis for 6 weeks. A rather large lobulated mass was seen on roentgen study of the chest in the left upper lobe area. Bronchoscopic examination and cytologic studies were negative. At thoracotomy, a large, smooth, lobulated tumor was found in the anterior segmental portion of the left upper lobe. The tumor appeared to infiltrate the mediastinum, the upper pericardium, and the phrenic nerve. A left upper lobectomy was carried out. The patient recovered from the operation but died 4 months later of a bleeding duodenal ulcer. At autopsy, tumor metastases showing both carcinomatous and sarcomatous elements were found in the retroperitoneal and mesenteric lymph nodes, the liver, the pancreas, the kidneys, and the adrenal glands. The sarcomatous element of the tumor appeared to be a fibrosarcoma. The microscopic appearance of the cells of the epithelial element strongly suggested peripheral (bronchiolar or alveolar) origin.

The published clinical experience with the more centrally located pedunculated endobronchial type of carcinosarcoma of the lung is quite different from that cited for the peripheral type (Table I). There appears to be a remarkable constancy in the clinical picture of the endobronchial type of tumor. All of the patients were men and all were in the fifth and sixth decades of

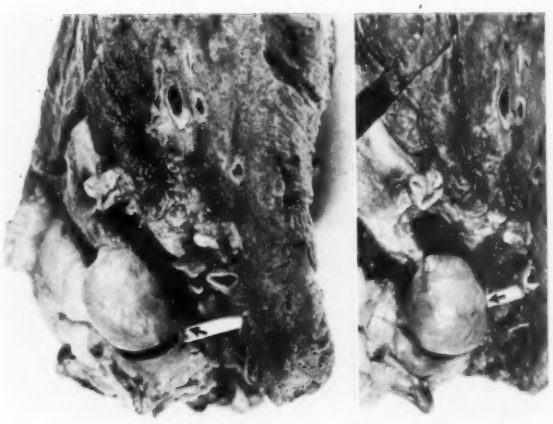

Fig. 3. Photographs of the formalin-fixed, cut right lower lobe taken from 2 angles to show the appearance of the terminal portion of one of the cylindrical, finger-like endobronchial growths *(arrow)* which had extended distally from the site of its pedunculated origin from the bronchial wall. Bronchial dilatation in the area of the endobronchial growth and distal bronchiectasis and consolidation also are shown. A section has been taken from the endobronchial growth.

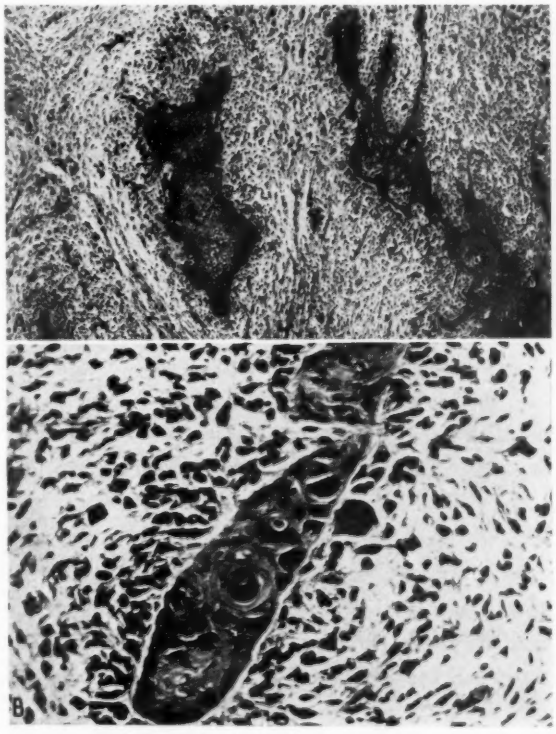

Fig. 4. Photomicrographs of the tumor under *A*, relative low power, and *B*, somewhat higher power from another area, illustrate the intermingling of the epithelial and the mesodermal elements of the carcinosarcoma. The epithelial element of the tumor is typical of epidermoid carcinoma. The stroma is fibrosarcoma.

Table I. *Summary of published clinical experience with endobronchial carcinosarcoma*

Author	*Age and sex*	*Clinical picture*	*Initial bronchoscopic biopsy*	*Bronchogram*
Bergmann and associates				
Case 1	51, M	Nonproductive cough for 1 yr., chest pain, WBC 22,000, lesion on chest roentgenogram, 20-pound weight loss		Filling defect, right upper lobe bronchus
Case 2	56, M	Chest pain, fever, malaise and 13-pound weight loss, lesion on chest roentgenogram	Negative for neoplasm	Filling defect, right upper lobe bronchus
Taylor and Rae				
Case 1	69, M	Nonproductive cough, fever and malaise, ill 2 mo., right lower lobe and middle lobe atelectasis on roentgenogram	Negative for neoplasm	
Case 2	57, M	Pain in chest, dyspnea and hemoptysis of 2 mo., 20-pound weight loss, left lung atelectasis on roentgenogram	Negative for neoplasm	
Moore	64, M	Pain in chest, cough and hemoptysis of 3 wk., right lower lobe lesion on chest roentgenogram	Negative for neoplasm	Filling defect, left lower lobe bronchus and bronchus intermedius, distal bronchiectasis

life. The major symptoms were nonproductive cough and chest pain. Fever, malaise, hemoptysis, and weight loss were encountered frequently.

Two of the patients were known to be smokers of cigarettes and 1 had never smoked. The endobronchial tumor mass was seen in all of the 4 cases in which bronchoscopy was carried out. However, the findings on initial bronchoscopic biopsy of the tumor mass proved consistently to be misleading. Initial bronchoscopic biopsy of the tumor mass in all 4 cases was reported as negative for neoplasm. In the first case of Taylor and Rae,[17] a second bronchoscopic biopsy taken 7 days after the initial attempt was reported as positive for malignant neoplasm (suggestive of sarcoma). In the second case of Bergmann and his associates, a positive biopsy for neoplasm was not obtained until the third bronchoscopic examination, 7 months after the initial attempt. In the interim, during which the diagnosis remained in doubt, a second unrewarding bronchoscopic examination and biopsy were undertaken and a thoracotomy was performed at which only drainage of a lung abscess was carried out. There also appears to be a hazard associated with the bronchoscopic biopsy of this type of tumor. The second patient of Taylor and Rae died of massive tracheobronchial hemorrhage 80 hours after bronchoscopic biopsy of the tumor had been performed.

In all of the 3 cases in which bronchograms were made, a filling defect in the bronchus was identified. In the case recorded here, bronchiectasis was demonstrated distal to the partially occluding bronchial mass. The radiopaque material in this case could be forced beyond the bronchial mass into the distal bronchial segments only with considerable difficulty.

Four of the patients with endobronchial carcinosarcoma were operated upon. Pneumonectomy was carried out in 3 and lobectomy in 1. All 4 patients recovered from the operation and all were alive without evidence of recurrence from 1 to 6 years after operation. The case reported here is, to the author's knowledge, the first recorded case of successful lobectomy for endobronchial carcinosarcoma of the lung.

The site of bronchial origin of the pedunculated endobronchial tumor was segmental or lobar in 4 of the 5 reported cases. In the second case reported by Taylor and Rae the tumor originated from the left main bron-

Cytologic study	*Origin of tumor*	*Regional node metastasis*	*Operation*	*Result*
—	Right upper lobe, apical segment bronchus	None	Pneumonectomy	Living 6 yr. after operation, no recurrence
Negative	Right upper lobe, lobar bronchus	None	Pneumonectomy	Living 1.5 yr. after operation, no recurrence
Negative	Right lower lobe, lobar bronchus	None	Pneumonectomy	Living 3 yr. after operation, no recurrence, some dyspnea
—	Left main bronchus	None	—	Died 80 hr. after bronchoscopic biopsy of tumor, death due to massive tracheobronchial hemorrhage, at necropsy tumor regarded as curable, no metastases found
Negative	Right lower lobe, basal segment bronchus	None	Lobectomy	Living 19 mo. after operation, working and asymptomatic, no recurrence

chus. From these observations, it is apparent the lobectomy was feasible in 4 of the 5 recorded clinical cases of endobronchial carcinosarcoma. Lobectomy is possible even in instances in which the endobronchial growth of the tumor has extended beyond the anatomic limits of the lobe of its pedunculated origin. Removal of the extended endobronchial growth can be achieved by means of the technique employed in the case recorded here; by removing briefly the noncrushing bronchus clamp and forcing out the unattached proximal segment of the endobronchial growth through the open end of the bronchial stump. This can be achieved by pressure exerted through the endotracheal tube by the anesthetist.

It is of interest and of prognostic significance that the regional lymph nodes were free of metastatic tumor involvement in all of the 5 recorded clinical cases of endobronchial carcinosarcoma. The patient of Taylor and Rae who died after bronchoscopic biopsy of the tumor also was found, on postmortem examination, to be free of distant metastases. Additional evidence of the seeming benignancy of these endobronchial tumors is to be found in the second case of Bergmann and his associates. In this case, 7 months elapsed between the initial diagnostic efforts and the final operative removal of the tumor. Nonetheless, this patient survived and had remained free of recurrence for 6 years at the time of their report.

The symptoms encountered in the endobronchial group of cases appear to result largely from the bronchial obstruction produced by the endobronchial tumor growth with distal atelectasis, bronchiectasis, suppuration, and abscess formation. The weight loss so frequently observed in these cases is probably due to acute and chronic pulmonary suppuration. The appearance of the bronchial tree distal to the endobronchial growth was not mentioned in the first case report of Bergmann and his associates. In their second case report, a pulmonary abscess had been found and drained at the time of the initial thoracotomy. Six months later, examination of the resected lung showed an intense acute bronchiectasis distal to the tumor. The bronchi were widely dilated with thinned-out walls and were filled with purulent material. In the first case of Taylor and Rae, bronchiectasis with an accumulation of purulent material was observed distal to the tumor. In their second case, an acute suppurative bronchitis was

found distal to the tumor. Pulmonary abscess, bronchiectasis, and considerable inflammatory reaction were encountered in the case recorded here.

Fibrosarcoma and squamous-cell carcinoma were the most frequently encountered cell types in the endobronchial group of carcinosarcomas. It is of interest that the gross appearance of these tumors is somewhat similar to the polypoid character observed in the limited published experience with pure pulmonary fibrosarcoma.[2]

Although reports of only 7 clinical cases of carcinosarcoma of the lung have appeared in the literature, it is probable that the true incidence of these unusual neoplasms is somewhat greater than the limited published experience indicates. Taylor and Rae reported their experience with 2 patients from 2 hospitals in Vancouver. The 2 cases of Bergmann and his associates were encountered in a series of 258 surgically removed bronchopulmonary tumors at the Barnes Hospital in St. Louis. It is hoped that additional case reports may help to establish more clearly the clinical picture and ultimate prognosis of these tumors.

SUMMARY

1. Thirteen cases of pulmonary carcinosarcoma of the lung have been reported. The literature pertaining to carcinosarcoma of the lung is reviewed. Seven of the cases were seen at autopsy and 6 were seen clinically.

2. A pedunculated endobronchial carcinosarcoma arising from a basal segmental bronchus of the right lower lobe of a 64-year-old white man is reported.

3. From an analysis of the published clinical cases, including the case reported here, it is apparent that there are 2 distinct types of pulmonary carcinosarcoma. In one type, the tumor is peripheral and solid. It may attain considerable size prior to detection and has a tendency toward direct invasion of adjacent chest wall and mediastinal structures. There is also a tendency toward distant metastasis and the prognosis is poor. Two of the clinical cases were of this type. The second type of tumor is more centrally located. It occurs as a pedunculated endobronchial growth with limited parenchymal extension from the site of its pedunculated origin from the bronchial wall. The tumor growth is largely endobronchial. The prognosis with this type of tumor is surprisingly good. Five of the clinical cases were of this type.

4. The symptoms associated with the solid peripheral type of tumor are due to the invasive and metastatic character of the neoplasm. Those of the endobronchial type result from bronchial obstruction with distal atelectasis, bronchiectasis, abscess formation, and acute and chronic suppuration.

5. The principal symptoms reported in cases of endobronchial carcinosarcoma are those of chest pain, cough, fever, malaise, hemoptysis, and weight loss.

6. Bronchoscopic biopsy and cytologic studies in the endobronchial group have proved to be uninformative and misleading. In addition, there appears to be some hazard associated with bronchoscopic biopsy of these tumors.

7. Pulmonary resection was carried out in 4 of the 5 patients with endobronchial carcinosarcoma seen clinically, pneumonectomy in 3 and lobectomy in 1. All 4 patients survived operation and all were reported to be alive and free of tumor recurrence from 1 to 6 years after operation.

8. The regional lymph nodes were free of tumor involvement in all of the 5 clinical cases of endobronchial carcinosarcoma. There was no evidence of tumor metastasis on postmortem examination of the patient who died of hemorrhage after bronchoscopic biopsy of the tumor.

9. The pedunculated origin of the endobronchial tumor was segmental or lobar in 4 of the 5 clinical cases.

10. From the observations described, it is apparent that lobectomy may be regarded not only as feasible, but as the operation of choice in the majority of cases of endobronchial carcinosarcoma of the lung, even when the endobronchial growth has extended beyond the anatomic limits of the lobe of origin.

11. The case reported here is, to the author's knowledge, the first recorded instance of successful lobectomy for endobronchial carcinosarcoma of the lung.

REFERENCES

1. Bergmann, M., Ackerman, L. V., and Kemler, R. L.: Carcinosarcoma of the lung, Cancer **4:** 919, 1951.
2. Black, H.: Fibrosarcoma of the bronchus, J. Thoracic Surg. **19:** 123, 1950.
3. Bösenberg, M.: Über Carcinosarkome, Ztschr. Krebsforsch. **36:** 416, 1932.
4. Cavallero, G.: Contributo allo studio dei tumori misti maligni del polmone di tipo bidermico (carcinosarcomi), Pathologica (Genova) **48:** 213, 1956.
5. Fischer, W.: Zur Kenntnis des lungenkrebse, Acta Unio internat. contra cancrum **3:** 221, 1938.
6. Frank, A.: Ein Karzinosarkom der Lunge, Schmidt's Jahrb. **322:** 149, 1915.
7. Graham, E. A., and Womack, N. A.: The problem of the so-called bronchial adenoma, J. Thoracic Surg. **14:** 106, 1945.
8. Hochberg, L. A., Grayzel, D., Benson, S. L., and Rosenberg, S.: Multiple primary tumors with fibrosarcoma and co-existing carcinosarcoma of the lung, Arch. Surg. **59:** 166, 1949.
9. Kika: Cited by Herxheimer, G., and Reinke, F., Ergebn. allg. path. Anat. **16:** 281, 1912.
10. Lavnikova, G. A.: Kartsinosarkoma legkogo, Vop. Onkol. **4:** 345, 1958.
11. Nowicki, W.: Carcinom und Sarkom als Kollisionsgeschwulst, Virchows Arch. path. Anat. **289:** 564, 1933.
12. Ogawa, K.: Uber eine Fall vom sehr seltenen primären Karzinosarkom der Lunge mit besonderer Berucksichtigung der histologischen Untersuchungen, J. Orient. Med. **11:** 133, 1929.
13. Peabody, C. N.: Carcinosarcoma of the lung of peripheral origin, J. Thoracic Surg. **6:** 766, 1959.
14. Pée, D.: Über einen Fall von Karzinosarkom der Lunge mit Kalkkugeln. Thesis, Christian-Albrechts Universität zur Kiel, Quakenbrück, 1936.
15. Saltykow, S.: Beiträge zur Kenntnig des Karzinosarkoms, Verhandl. deutsch. path. Gesellsch. **17:** 351, 1914.
16. Selye, H.: Über zwei bemerkenswerte Falle von Karzinosarkom, Med. Klin. **24:** 1197, 1928.
17. Taylor, H. E., and Rae, M. V.: Endobronchial carcinosarcoma, J. Thoracic Surg. **24:** 93, 1952.
18. Weber, F.: Ein Karzinosarkom der Lunge, Zentralbl. allg. Path. Anat. **72:** 113, 1939.

Subglottic carcinoma with extensive tracheal involvement

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Carcinoma arising in the subglottic portion of the larynx, especially when the lesion extends below the first tracheal ring, presents special problems in diagnosis and surgical treatment. These are illustrated in the case report that will be presented. A technique devised for the formation of a tracheostomy will be described.

More than 80 years ago, Isambert[5] first differentiated these tumors from other laryngeal carcinomas. In 1881, Delavan[4] was the first to describe a case occurring in this country. Although extension into the trachea is rare, subglottic carcinoma is not uncommon. Thomson[12] classified 26 per cent and Clerf[1] 10 per cent of intrinsic carcinomas in the subglottic category.

These lesions originate on the lower surface of the vocal cord or apart from the cord, sometimes as low as the cricoid ring. The tumor is commonly located in the middle or anterior part of the larynx. It may spread across the midline or through the cricothyroid membrane, and may metastasize to the lymph nodes over this area. The isthmus of the thyroid gland can also be directly invaded. At the onset of symptoms, the only complaints may be difficulty in expelling sputum, weakness of voice, or a sore throat. In other cases, the gradual onset of dyspnea or stridor on exertion may be the first symptom. When the cord becomes secondarily involved by upward extension of the tumor, hoarseness occurs as a late symptom.

The diagnosis is made by direct laryngoscopy and biopsy. Since the subglottic area is often difficult to visualize, the full extent of the lesion may not be appreciated. When immobility of the vocal cord is not justified by the size of the visible growth, subglottic involvement is suggested. Earlier surgeons advocated exploratory thyrotomy prior to resection in order to determine the extent of the lesion. More recently, laryngeal tomography has been used to demonstrate the contours of the subglottic region and when the tumor is large enough to be visualized, this can provide an accurate evaluation of the growth. Knowledge of more superficial extensions, however, is still best provided by direct visualization at operation. It is essential to divide the trachea at a low level in order to insure the widest possible resection. When tracheotomy is indicated prior to operation, it must also be performed at the lowest level.

The incidence of metastases is higher in subglottic malignancy than in cordal carcinoma because of the abundant lymphatics of the subglottic area. Prognosis is, therefore, poor. According to Orton,[9] the possibility of cure diminishes with the extent of the growth away from the vocal cords. The mortality rate reported ranges from 40 to 50 per cent.[2, 9, 12] These figures are considerably higher than those for intrinsic carcinomas. Jackson and Jackson[6] report a sur-

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vival rate for intrinsic carcinomas of 75 to 80 per cent; in small lesions, the 5-year cure may rise as high as 90 per cent.

Laryngectomy, with the addition of radical neck dissection when indicated, has been the surgical approach to subglottic carcinoma. When the trachea is involved, most authors have believed that the prognosis is hopeless and the lesion inoperable because of extension of the disease between the trachea and the esophagus and invasion of the mediastinal lymphatics. Clerf[3] considers inoperable any lesions which extend below the first tracheal ring. Jackson and Jackson consider operation contraindicated when there is involvement below the second tracheal ring. On the other hand, Thomson records a tumor that necessitated the removal of the first 3 cartilaginous rings; nevertheless the procedure resulted in long-term control of the disease. Thus, it appears that the value of operative procedures in extensive subglottic lesions has not been fully assessed, and that techniques for the management of these lesions should be developed.

CASE REPORT

History. The patient was a 66-year-old white man who was admitted on Dec. 3, 1958, because of hoarseness of 7 months' duration. During that period, there also had been gradually increasing dysphagia, anorexia with occasional vomiting, and a weight loss of 20 pounds. In the last few days prior to admission, only liquids could be swallowed.

Physical examination. There was evident cachexia and dehydration. No abnormalities were present in the mouth and pharynx, and there was no cervical lymphadenopathy. The chest was emphysematous with considerable dorsal kyphoscoliosis. On direct and indirect laryngoscopy, a tumor of the entire right vocal cord was seen extending in a subglottic direction. The cord moved only a slight degree. Biopsy showed squamous-cell carcinoma.

Results of urinalysis, blood count, electrocardiogram, and blood chemistry determinations were normal. The chest roentgenograms showed no pleural or pulmonary pathologic process. Soft-tissue films of the neck demonstrated osteoarthritic changes of the cervical spine. Laryngeal tomography revealed a tumor mass in the subglottic region with involvement of the right vocal cord.

Course in hospital. Because the patient was unable to swallow, tube feedings were started immediately after admission. It was evident that even if the lesion were operable, long preparation would be required for the operation. Therefore, radiation therapy was given and completed by Jan. 28, 1959. A dosage of 6,400 r was administered in 31 days. Swallowing improved somewhat, but not enough for discontinuation of the tube feedings.

Subsequent laryngoscopy showed fixation of the right vocal cord and a small subglottic nodule 3 to 4 mm. in size was seen below the anterior commissure. Biopsy at this time failed to show residual carcinoma. However, a subsequent biopsy of the subglottic area below the right cord showed squamous-cell carcinoma.

Since the patient's general condition was now adequate, a wide-field laryngectomy was performed on March 20, 1959. The trachea was transected below the third ring, but when the mucosal surface was examined, several discrete, raised, pearly gray, umbilicated plaques, the largest of which was 3 mm. in diameter, were seen on the posterior wall. These lesions extended to the level of the fifth tracheal ring. After removal of the larynx, the remainder of the involved trachea was excised beyond the most distal implant. As a result, the shortened trachea could not be sutured to skin in the usual manner. A skin flap was fashioned into a circular tube and approximated to the trachea.

Pathology confirmed the presence of subglottic carcinoma with tracheal extension and distal tracheal implants. The immediate postoperative course was satisfactory. There was a small area of slough at the sutured corners of the skin tube, but this soon healed. Four weeks after operation the patient was discharged. At that time, he was eating well and the tracheostomy stoma required minimal care. A tracheostomy tube was worn continuously to prevent constriction.

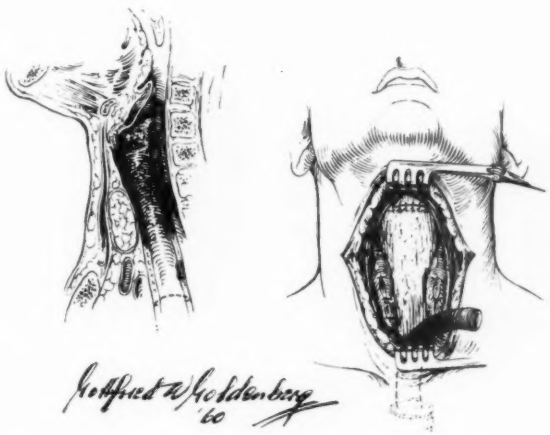

Fig. 1. Drawings indicate the extent of the tumor, the level of tracheal amputation, and closure of the pharynx.

Subsequent course. At first, there was a gain in weight and apparent good health. However, 4 months after operation, a fixed, firm mass developed on the left side of the neck just beneath the incision. Tumor was also observed within the pharynx at the suture line. There was no recurrence of tumor in the trachea or skin tube. Additional radiation therapy was given, but the patient's condition continued to deteriorate and he died of the disease on Feb. 10, 1960, approximately 10 months after laryngectomy.

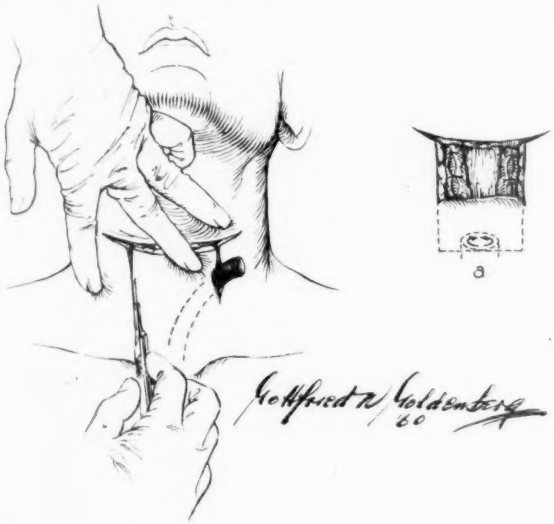

Fig. 2. Two parallel vertical incisions are made with utilization of the middle third of the lower skin flap, which is turned down to join the tracheal stump.

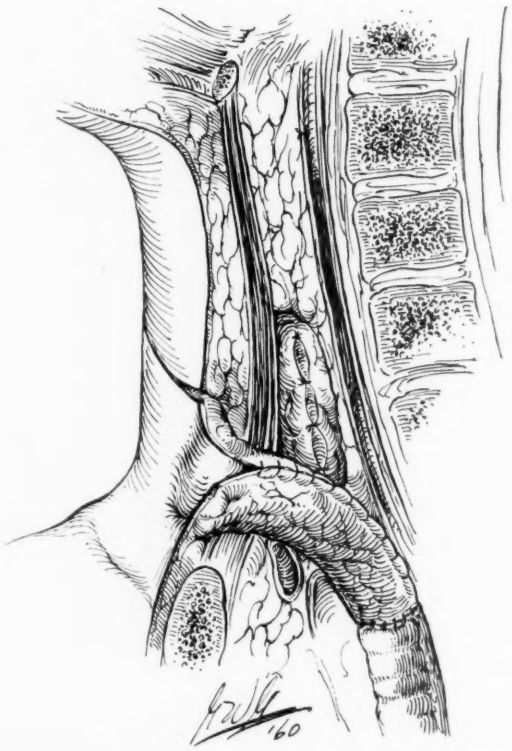

Fig. 3. Formation of the skin tube which is sutured to stump of trachea.

TECHNIQUE

The technique used requires a standard transverse laryngectomy incision and the absence of a previous tracheostomy. In the case reported, skin flaps, including the platysma muscle, were raised and laryngectomy was carried out. The level of the tracheal incision and the level of the remaining tracheal stump are illustrated in Fig. 1. Closure of the pharynx was carried out transversely. A skin tube was then prepared for suture to the trachea. Two parallel vertical incisions were made in the middle third of the lower flap. The distance between the incisions equalled the circumference of the trachea. Their length equalled half the distance between the transverse skin incision and the tracheal stump (Fig. 2). In this case, the incisions were 2 inches long and 2 inches apart, giving the flap a 1 to 1 ratio of length to base, which insured an adequate blood supply. This flap was turned downward and inward, and the distal edge was sutured accurately to the tracheal mucosa with interrupted fine catgut stitches (Fig. 3). The anastomosis was started anteriorly and continued around the trachea until the opposite corners of the skin flap were approximated to each other at the midline posteriorly. The suturing was then continued upward to join the parallel edges of the flap, forming a tube with the suture line in back. After completion of the skin tube, the remainder of the laryngectomy incision was closed in the form of a T. There was no difficulty in approximating the lateral thirds of the lower flaps of this incision because of the defect left by the removal of the larynx. The upper flap was then a third longer than the lower, and this required accurate placement of the sutures to secure an even closure (Fig. 4). The final appearance of the healed tracheostomy is illustrated in Fig. 5.

DISCUSSION

The method used in this case for construction of a tracheal stoma was not previously described. This technique was made possible by a transverse incision and by the absence of a preoperative tracheostomy. As a solution of the problem presented, it proved quite satisfactory. A method of bringing skin to trachea in the presence of a previous tracheostomy was reported by Watson.[14] In that report, the trachea was resected for a carcinoma which appeared at the point of irritation caused by the continuous use of a tracheostomy tube for 15 years. This procedure also produced a good initial result.

In planning a very low tracheostomy, there are several possible approaches. The best method is to bring the skin down to the undisplaced trachea without resection of the sternum; the other methods involve removal of overlying bone to produce a thoracic tracheostomy. Attempts at the latter approaches have been generally unsatisfactory.

In resection of a carcinoma recurrence at a tracheostomy stoma, Kleitsch[7] transected the manubrium and inserted a polyethylene tube into the trachea just above the innominate artery. Death from hemorrhage occurred in 4 months because of erosion by the tube into the innominate artery. In a similar case, Minor[8] split the sternum and dissected the mediastinal trachea from surrounding structures. The trachea was then angulated forward and secured to the periosteum of the sternum. A skin flap was then used to complete the stoma. Two and one-half months later, this patient also died from massive hemorrhage within the substernal space. Saareste[11] also lost a patient 9 days after a mediastinal tracheostomy because of hemorrhage from the innominate artery. Most recently, Waddel and Cannon[13] revised and extended Minor's technique. They similarly utilized a skin flap from the anterior chest wall which was brought through a hole rongeured at an appropriate site in the sternum. Here, too, it is admitted that the trachea is unavoidably held forward under tension. Two of the 4 patients in which this procedure was carried out died of massive hemorrhage from erosion of one of the great vessels of the chest. In one of these patients, this catastrophe occurred 3 months after discharge from the hospital.

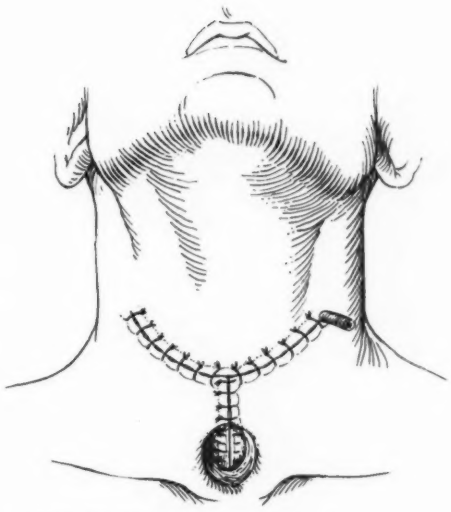

Fig. 4. The incision is closed as a T.

Fig. 5. Appearance of skin-tube tracheostomy after healing.

It is evident from these experiences that anterior displacement of the mediastinal trachea or the use of a rigid tube emerging through the sternum is likely to produce pressure on the innominate artery or other great vessels with subsequent erosion and hemorrhage. Therefore, the method of fashioning a skin tube to anastomose to the undisturbed tracheal stump within the thorax is preferable. It produces no tracheal displacement; the tracheostomy tube supported

by the manubrium cannot cause pressure on the innominate artery.

SUMMARY

1. Diagnostic and surgical features of subglottic laryngeal carcinoma are reviewed. A case of extensive tracheal involvement is reported.

2. A technique for the construction of a skin-tube tracheostomy is described and illustrated.

3. The hazard involved in thoracic tracheostomy is discussed.

REFERENCES

1. Clerf, L. H.: Cancer of the larynx: an analysis of 250 operative cases, Arch. Otolaryng. **32:** 484, 1940.
2. Clerf, Louis H.: Laryngectomy, Surg. Gynec. & Obst. **86:** 197, 1948.
3. Clerf, L. H.: Subglottic carcinoma of the larynx, Pennsylvania M. J. **42:** 527, 1948.
4. Delavan, B.: Primary epithelioma of larynx below vocal cords: unique case, New York M. Rec. **20:** 625, 1881.
5. Isambert, E.: Contributions á l'étude du cancer laryngé, Ann. d. mal. de l'oreille, du larynx **2:** 1, 1876.
6. Jackson, C., and Jackson, C. L.: Cancer of the larynx, Philadelphia, 1939, W. B. Saunders Company.
7. Kleitsch, W. P.: Anterior mediastinal tracheotomy, J. Thoracic Surg. **24:** 38, 1952.
8. Minor, G. R.: Transternal tracheal excision for carcinoma, J. Thoracic Surg. **24:** 88, 1952.
9. Orton, H. B.: Cancer of the larynx, immediate and ultimate results in 102 operative cases, Tr. Am. Laryng. A. **60:** 144, 1938.
10. Orton, H. B.: Surgery of carcinoma of the larynx, A. M. A. Arch. Otolaryng. **64:** 205, 1956.
11. Saareste, F.: Difficult intubation on account of functional laryngeal stenosis after superior tracheostomy for laryngeal diphtheria; death from hemorrhage of the innominate artery nine days after inferior tracheotomy, Monatsschr. Ohrenh. **64:** 1996, 1931.
12. Thomson, St. Clair: Subglottic cancer of the larynx, J. Laryngol. & Otol. **52:** 803, 1937.
13. Waddel, W. R., and Cannon, B.: A technique for subtotal excision of the trachea and establishment of a sternal tracheotomy, Ann. Surg. **149:** 1, 1959.
14. Watson, W. L.: Cancer of the trachea fifteen years after treatment for cancer of the larynx, J. Thoracic Surg. **12:** 142, 1942.

Surgical treatment of nasal hemorrhage

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Profuse nasal hemorrhage often produces shock and occasionally causes death. Lying deep within the nasal chamber near the origin of the regional artery, the bleeding site is almost impossible to identify because of its inaccessibility to inspection and because of the continued outpouring of blood. Between episodes of bleeding, little or nothing may be found to reveal the source, even on careful examination with the electric nasopharyngoscope.

Any hemorrhage which causes an appreciable fall in blood pressure may produce coronary occlusion in elderly patients. One such case resulting from epistaxis was reported by Bean,[1] whose review of 300 cases of coronary occlusion demonstrated the importance of preventing shock in patients with hypertensive cardiovascular disease. A fatal case of epistaxis from the anterior ethmoid artery was reported by Macbeth.[8]

Most nasal hemorrhages can be controlled by nasal packing combined with the use of sedation, hypnotics, and various medications such as estrogens, vitamin K, and so forth. Particularly effective in posterior nasal hemorrhage are the packs described by Saunders,[12] made of a vaginal tampon, and by Woodruff,[16] who packs cotton tightly under the posterior end of the inferior turbinated bone.

Unfortunately, postnasal packing is not only uncomfortable, but it also frequently causes complications, even though the patient is receiving antibiotics. Purulent sinusitis is not unusual, nor are ear complications such as hemotympanum or, less often, otitis media. Fissures or lacerations may occur where the anchoring silk string contacts the external nares or soft palate.[7] Osteomyelitis of the base of the skull resulting from a tight postnasal pack was reported by Spar and Williams.[15]

In 4 to 8 per cent of hospitalized patients, the packing and medical measures do not control the bleeding, and surgical intervention becomes necessary. This may consist of submucous resection of the nasal septum or of blood-vessel ligation. Removing a deviated portion of the septum allows better inspection, easier packing, and a release of tension over sharp crests or spurs. This procedure alone may allow the bleeding vessel to contract and heal. The operation can quite easily be combined with ligation of the anterior ethmoid artery if necessary.

As in other locations, ligation of the regional artery is the most effective method of controlling hemorrhage. Terminal branches of the internal and external carotid arteries supply the nasal mucosa. The anterior superior portion of the nasal chamber is supplied by the internal carotid through its anterior ethmoid branch of the ophthalmic artery. The posterior inferior portion below the middle turbinated bone is supplied by the sphenopalatine branch of the external carotid artery. Terminal branches of the latter vessel anastomose at Kiesselbach's triangle with branches of the superior labial artery. The posterior ethmoid, also a branch of the ophthalmic artery, is usually ascribed a minor role in epistaxis because of its usual small size. Studies of cadavers, however, show that it is sometimes a sizable vessel, one which might be responsible for continued postnasal bleeding after ligation of the external carotid.[2]

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Table I. *Data on 16 patients who underwent blood-vessel ligation for epistaxis, 1952 through 1959*

Case No.	*Age, race, and sex*	*History and associated conditions*	*Indications*	*Ligation site and date*	*Postoperative course*
1. M. S.	50, WF	Hypertension, nosebleed and cauterization 15 yr. ago	Continued bleeding after 16 transfusions	Right external carotid Jan. 22, 1952 Left external carotid Jan. 25, 1952 Right anterior ethmoid Jan. 29, 1952	Left pansinusitis Bleeding recurred 2 yr. later requiring postnasal pack
2. J. D.	62, WM	Hypertension, arteriosclerosis, liver disease	Shock, continued bleeding for 2 wk.	Right external carotid Mar. 31, 1952 Right anterior ethmoid Apr. 3, 1952	No further bleeding Right pansinusitis
3. M. P.	57, WF	Rheumatic heart disease, hemiparesis	Shock on admission	Left external carotid Mar. 18, 1953	No further bleeding
4. J. D.	52, WM	Alcoholism, hypertension (reserpine)	Pulse 120, Hb. 7.2 Gm., RBC 2.48, Hct. 26	Left external carotid June 24, 1953 Submucous resection and left anterior ethmoid Feb. 28, 1955	One minor epistaxis in Kiesselbach's area 3 mo. later, none since
5. C. Z.	32, WM	Smoker (1 pack per day)	7 pints blood transfused in 9 days, Hb. below 7.5 Gm., pulse 118	Left external carotid July 10, 1953	No further bleeding
6. S. S.	54, WF	Hypertension, smokes 1 pack per day	6 pints blood transfused in 6 days, Hb. 8 Gm.	Left external carotid Jan. 9, 1954	No further bleeding
7. W. G.		Hypertension (reserpine), polypectomies and ethmoidectomies in 1944	Shock, Hb. 8.2 Gm., bleeding 1 wk.	Right external carotid July 22, 1954	Epistaxis, right, 2½ yr. later, BP 230/110, controlled by pack
8. S. S.	49, WM	Ethmoidectomy 24 yr. ago	Hb. 8.6 Gm. after 2 wk. treatment	Left anterior ethmoid Aug. 14, 1954 Left posterior ethmoid	None further
9. G. B.	55, WM	Diabetes, obesity, hypertension, alcoholism	Continued bleeding in spite of packs for 2 wk. and transfusion, Hct. below 28	Submucous resection Feb. 26, 1955 Left external carotid Feb. 28, 1955	No further bleeding
10. J. D.	52, WM	Alcoholism, fatty infiltration of liver, congenital heart failure	1 wk. recurrent bleeding, Hb. 9.5 despite 1,000 ml. blood	Right external carotid Dec. 22, 1955	None further
11. J. L.	61, WM	Polyps in right ethmoid area, recurrent nosebleeds for 2 yr.	6 episodes in past 12 hr.	Right anterior ethmoid June 16, 1958	Profuse right epistaxis, 1 yr. postoperative, minor epistaxis 15 mo. postoperative, none reported in past year
12. A. S.	69, WM	Alcoholism, bad septal deviation	Hct. 34 to 27, intermittent epistaxis for 12 days	Right ethmoid Submucous resection Sept. 29, 1958	No further bleeding

Table I.—*Cont'd*

Case No.	*Age, race, and sex*	*History and associated conditions*	*Indications*	*Ligation site and date*	*Postoperative course*
13. T. R.	37, WM	Hypertension, alcoholism, syphilis, 9 previous admissions for lacerations incurred in falls (drunk)	Hct. 17 despite 1,000 ml. blood in 24 hr.	Right anterior ethmoid Oct. 8, 1958 Right exterior carotid Oct. 10, 1958	No further bleeding
14. A. B.	56, WM	Smokes 1½ packs per day, septal deviation to left	2 mo. recurrent epistaxis	Submucous resection Left anterior ethmoid Dec. 22, 1958	1 yr. later, left sided hemorrhage, easily controlled by pack 2 days
15. C. C.	66, WM	Hypertension, alcoholism, smokes 2 packs per day, badly deviated septum, chronic lung disease	10 days' bleeding, bad septal deflection, Hct. 22	Submucous resection, right anterior ethmoid Mar. 4, 1960 Right external carotid Mar. 11, 1960	No further bleeding reported
16. A. C.	47, WF	Hypertension, menopause, Laennec's cirrhosis	Bleeding 1 to 3 times per day for 6 mo., repeated cauterizations	Left anterior ethmoid July 1, 1960	Palpebral hematomas, bilateral, no further bleeding

After Flemming's[3] first successful ligation of the common carotid in 1803, this vessel was occasionally ligated for intractable nasal hemorrhage. However, common carotid ligation results in only a 50 per cent decrease in normal flow as a result of the retrograde circulation down the external carotid artery.[14] The more effective and less hazardous ligation of the external carotid for nasal hemorrhage was not reported until 1925 by Hyde,[5] although 2 cases attributed to Jackson were mentioned in McKnight's report of 1926.[9]

Although the regional artery may be ligated in any of 5 locations, the 2 usual sites for ligation are the external carotid above the superior thyroid branch and the anterior ethmoid artery as it enters its foramen in the orbit. Other less common ligation sites are the septal branch of the labial artery, which can be sutured according to Rosenvold's technique as it enters the floor of the nasal vestibule and is used for the rarely intractable anterior septal bleeding[11]; the internal maxillary, which can be ligated after the anterior and posterior walls of the maxillary sinus are opened as described by Seiffert in 1929[13]; and the sphenopalatine artery itself, accessible to ligation by Silverblatt's technique, after the ethmoid cells are exenterated.[14]

MATERIAL

During the 8 years between January, 1952, and December, 1959, 210 patients were admitted to New Haven Hospital for severe nasal hemorrhage. During this same period 23 blood-vessel ligations were carried out in 16 patients for intractable spontaneous hemorrhage (Table I). Patient 1 was treated at one of our affiliated hospitals, but is not included in the statistical analysis. Other ligations for bleeding associated with injuries, neoplasms, and familial hemorrhagic telangiectasia are not included in this study. Seven per cent of all patients admitted for epistaxis were treated by ligation as compared to 8 per cent in Hallberg's[4] series of 212 and 4.5 per cent of the adults in the series of Ogura and Senturia.[10]

Age. Of the 210 patients admitted for epistaxis, 99, or nearly half, were between the ages of 50 and 69. The largest single group was between 50 and 59 years of age (Fig. 1).

Month. Nasal hemorrhage appears to be

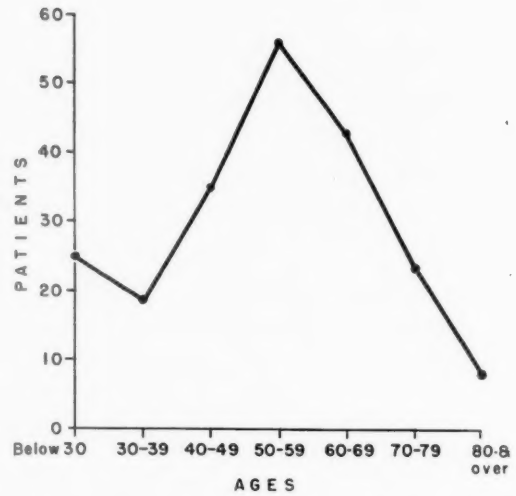

Fig. 1. Ages of 210 patients admitted for epistaxis (1952 through 1959).

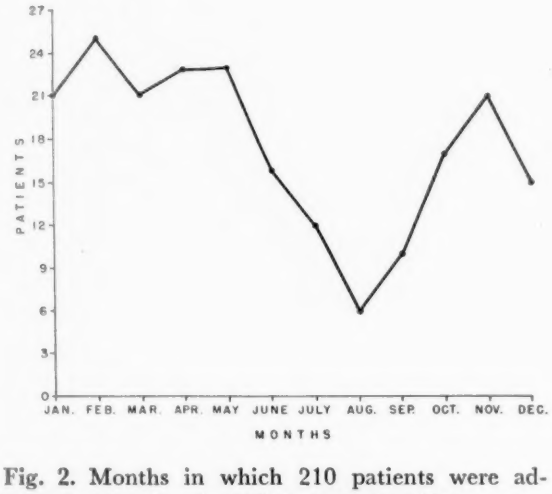

Fig. 2. Months in which 210 patients were admitted for epistaxis (1952 through 1959).

a winter condition. Most of our patients were admitted during the months in which artificial heat is necessary in the home. That this is a factor is suggested by the infrequency of nasal hemorrhage in milder climates where central heat is not used (Fig. 2).

Associated conditions. Nine of the 16 patients were hypertensive. At least 2 of these were under treatment with reserpine. Whether or not the nasal congestion which frequently results as a side effect of reserpine treatment contributed to the bleeding is an interesting speculation. Six of the 16 patients were alcoholics, either so diagnosed on previous hospital admissions or as estimated by the quantity of daily intake. Two patients had undergone previous ethmoidectomies, one 10 years previously and one 24 years previously.

INDICATIONS

Repeated severe hemorrhage. Most of the 210 patients admitted for epistaxis continued to bleed for from 5 to 7 days in spite of all medical measures. Blood loss, however, was not excessive according to hematocrit and blood pressure determinations. Of the 16 patients who required blood-vessel ligation, 9 had bled for more than 1 week. After this length of time, the patient is usually disheartened by his lack of progress and is extremely reluctant to undergo any further postnasal packing. Repeated transfusions were given in most cases (Patient 1 required 16 pints of whole blood).

Impending or actual shock. A hypertensive patient who has suffered a substantial loss of blood may exhibit a blood pressure within normal limits on admission. Such a level may, however, be dangerously low in his case.

SELECTION OF VESSEL FOR LIGATION

It is important to determine whether the bleeding is from high in the nose or low. The high bleeding vessels generally tend to be located anteriorly and the low ones posteriorly. With profuse hemorrhage, however, it may even be difficult to determine which side of the nose is the source. Five of our patients required ligation of a second vessel within a few days because the wrong arterial system had been tied off. Continued bleeding is almost never due to anastomotic connections.

TECHNIQUE

Local anesthesia is used because of its simplicity, because of the danger of aspiration of blood under general anesthesia, and because the patients usually present poor risks for general anesthesia.

The external carotid artery is exposed by means of an incision along the anterior border of the sternocleidomastoid muscle ex-

tending from the midpoint of the thyroid cartilage to the level of the angle of the mandible. The facial vein and hypoglossal nerve cross the artery and must be identified. The external carotid can be distinguished from the internal by its branches. It should be ligated between the superior thyroid and lingual branches, so that the blood flow through the proximal portion of the external carotid into the superior thyroid will prevent retrograde thrombosis into the internal carotid. With the exception of 1 case in which 3 ligatures were placed on the vessel without dividing it, 1 single ligature has been placed between the superior thyroid and lingual branches of the external carotid artery. While a single ligature carries with it the theoretical risk of necrosis of the vessel wall and subsequent hemorrhage, this has not occurred in our series.

The anterior ethmoid artery is ligated at its foramen where the vessel branches from the ophthalmic artery. An incision is made halfway between the inner canthus of the eye and the midline of the nose, extending slightly into the eyebrow. Incision is carried to the bone through the periosteum, the latter being elevated to expose the frontolacrimal suture. This suture line is followed back by elevation of the orbital periosteum until the anterior ethmoid foramen is seen, where the artery, vein, and nasociliary nerve enter in a common bundle. The foramen is found in the frontal-ethmoid suture line or immediately above it.

Because the anterior ethmoid bundle is short and is located deep within the orbit, there may be considerable difficulty in placing a ligature around it, especially if the usual surgical instruments are used. Therefore, a neurosurgical clip may be applied to the vessel, or a long ligature carrier may be fashioned by wedging the point of a small cutting-edge needle into the end of a spinal needle, crimping it in place with a heavy hemostat, then bending the suture-carrying end into an arc small enough to encompass the artery (Figs. 3 and 4).

If the vessel is ligated, a single tie should be used for several reasons. First, the neurovascular bundle entering the foramen is so short that any effort to expose it sufficiently to allow the placement of 2 ligatures may tear the vessel and result in uncontrollable bleeding. Another reason for a single tie is the possibility of the second ligature's slipping off the vessel's short pedicle. Kulvin reported his experience in dividing the ethmoid artery between ligatures and encountering proptosis of the eye postoperatively as a result of bleeding. Exploration of the orbit revealed that the lateral ligature had slipped off the vessel and the artery had retracted and bled into the orbital cone.[6] If one is unfortunate enough to encounter bleeding from the ethmoid bundle during efforts to expose or ligate it, he can safely control the bleeding by electrocoagulation. However, it is prob-

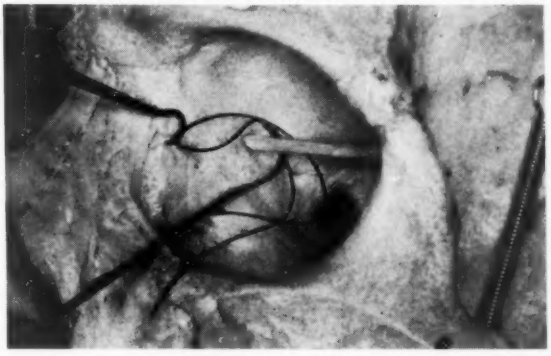

Fig. 3. Ligature has been passed around the anterior ethmoid neurovascular bundle, represented by the applicator entering the anterior ethmoid foramen. Ligature is then grasped by hook.

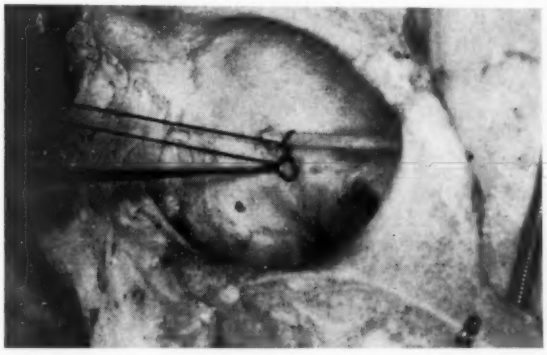

Fig. 4. Ligature has been tied and the knot drawn tight by passing the lower silk through a smooth ear curette. Ferris-Smith knot tier is similar and is used in this fashion.

ably well to avoid cauterizing the posterior ethmoid as is sometimes recommended, because of its proximity to the nearby optic nerve (2 to 3 mm.).

COMPLICATIONS

Except for 1 case of bilateral palpebral hematomas and 1 minor stitch abscess, there were no complications in the 23 blood-vessel ligations. This contrasts sharply with the high incidence of complications in postnasal packing, even though these are usually minor.

RESULTS

Immediate results were excellent, with prompt control after the proper vessel had been ligated. Late results were of interest in that 2 patients suffered recurrence of bleeding from the same side 2½ years later, 2 patients had a recurrence from the same side 1 year later, and 1 suffered a minor recurrence 1 month after ligation, but has had none in the past 5 years. The recurrences were usually easy to control, either by packing or by electrocautery at the bleeding site.

DISCUSSION

The low incidence of complications with blood-vessel ligation in this and other series, contrasted with high incidence with postnasal packing, suggests that some of the 93 per cent who recovered on medical management might better have been treated by ligation, so as to spare them unnecessary discomfort and suffering. In this regard, it is interesting that the percentage of ligations among large reported series of patients hospitalized for nasal hemorrhage in various medical centers is relatively similar, 4 to 8 per cent.

CONCLUSIONS

Profuse bleeding from deep within the nasal cavity may produce shock and endanger life. About 7 per cent of all patients admitted for severe nasal hemorrhage in this series of 210 hospitalizations failed to respond to packing and the usual measures. Ligation of the anterior ethmoid or the external carotid artery in this group controlled the bleeding promptly.

REFERENCES

1. Bean, W. B.: Infarction of heart: morphological and clinical appraisal of 300 cases: predisposing and precipitating conditions, Am. Heart J. **14:** 684, 1937.
2. Flemming: Quoted by Spar, A. A., and Hallberg, O. E.: Severe epistaxis and its management: report of eleven cases in which the external carotid artery was ligated, Ann. Otol. Rhin. & Laryng. **56:** 141, 1947.
3. Hallberg, O. E.: Severe nosebleed and its treatment, J. A. M. A. **148:** 355, 1952.
4. Hyde, F. T.: Ligation of the external carotid artery for the control of idiopathic nasal hemorrhage, Laryngoscope **35:** 899, 1925.
5. Kirchner, J. A., Yanagisawa, E., and Crelin, E.: Surgical anatomy of the ethmoidal arteries, A. M. A. Arch. Otolaryng. In press.
6. Kulvin, M.: Epistaxis, control by ligation of anterior ethmoid artery, A. M. A. Arch. Otolaryng. **62:** 84, 1955.
7. Kuhn, A. J., and Hallberg, O. E.: Complications of postnasal packing for epistaxis, A. M. A. Arch. Otolaryng. **62:** 62, 1955.
8. MacBeth, R. G.: Anterior ethmoidal hemorrhage, Proc. Roy. Soc. Med. **40:** 280, 1947.
9. McKnight: Quoted by Spar and Hallberg.[3]
10. Ogura, J. H., and Senturia, B. H.: Epistaxis, Laryngoscope **59:** 743, 1949.
11. Rosenvold, L. K.: Intranasal ligation for epistaxis, Arch. Otolaryng. **32:** 1109, 1940.
12. Saunders, W.: Effective control of postnasal hemorrhage, A. M. A. Arch. Otolaryng. **64:** 291, 1956.
13. Seiffert, A.: Unterbindung der Arteria Maxillaris Interna, Ztschr. Hals-Nasen-u. Ohrenh. **22:** 323, 1929.
14. Silverblatt, B. L.: Epistaxis—evaluation of surgical care, Laryngoscope **65:** 431, 1955.
15. Spar, A. A., and Williams, H. L.: Osteomyelitis of the basisphenoid and basiocciput with meningitis and cranial nerve palsies as a complication of nasopharyngeal packing for control of epistaxis, Arch. Otolaryng. **46:** 473, 1947.
16. Woodruff, G. H.: Cardiovascular epistaxis and the naso-nasopharyngeal plexus, Laryngoscope **59:** 1238, 1949.

The kidney and regional hypothermia

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The search for methods which would permit open-heart operations focused attention on hypothermia induced by surface cooling approximately a decade ago. Because of dangers of cardiac arrhythmias during general hypothermia (26 to 28° C.), regional cooling of isolated organs has recently achieved clinical prominence.

Interest in regional hypothermia of the kidney has been stimulated by the demonstration of a protective effect by hypothermia on the kidney during prolonged ischemia.[7, 16, 26, 27] Recently, emphasis has centered on development of more efficient means of obtaining rapid heat transfer.[7, 8, 28]

EFFECT OF ISCHEMIA ON RENAL FUNCTION

Numerous studies have confirmed the presence of impaired kidney function after prolonged ischemia. In unilaterally nephrectomized rats,[17] 2-hour occlusion of the renal artery of the remaining solitary kidney is well tolerated. Three hours of ischemia results in a 50 per cent mortality rate. In rabbits with only 1 kidney,[1] renal artery clamping for 2 hours is uniformly fatal. Sheep[18] tolerate 1½ hours of renal ischemia after contralateral nephrectomy.

Controversial findings in dogs are worth mentioning. Friedman and his associates[13] reported negligible depression in renal function after obstruction of the renal artery for 2 hours, which confirms earlier observations of Hamilton and his co-workers.[14] In a small series of dogs, Roof and her associates[24] clamped the renal artery for 2 hours and reported permanent depression in function (50 to 70 per cent of preoperative levels). Birkeland and his group[4] occluded the renal artery of dogs for 3 hours at normal temperature with uniformly fatal results.

Scheibe and associates[25] occluded the renal pedicle and compared this series with one in which the dog's renal artery alone was clamped; less renal damage was noted when the artery alone was clamped.

Data from patients in whom the renal artery was occluded is scanty and inconsistent. Estimates of a safe period of renal artery occlusion vary from 30 minutes to several hours. Bahnson[2] reported the case of a patient who died in uremia 4 days after resection of an aortic aneurysm which had required occlusion of the aorta above the renal arteries for 110 minutes. Another of his patients[3] survived renal artery ischemia for 37 minutes. Semb[27] occluded the renal artery for 90 minutes without evidence of renal damage. Ellis and colleagues[12] resected

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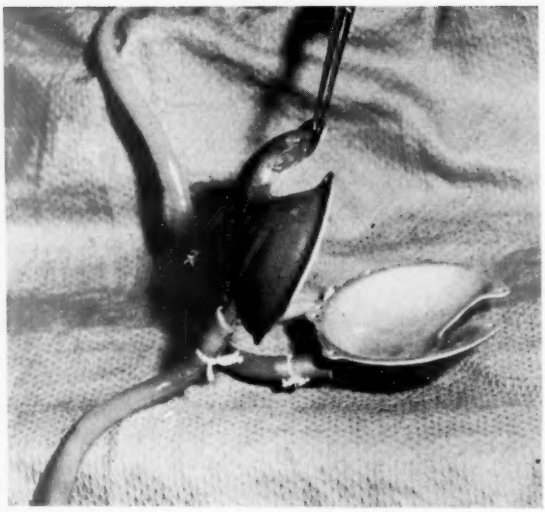

Fig. 1. The stainless steel kidney cooler.

an abdominal aortic aneurysm which involved the right renal artery. Ninety-five minute occlusion of the renal artery resulted in temporary loss of function. An intravenous pyelogram was reported as normal 2 weeks after operation. Creech and co-workers[9] resected aneurysms of the upper abdominal and thoracic aorta and occluded the latter vessel for intervals of up to 60 minutes. No significant reduction in renal function was described. In another report by these authors[10] the aorta and renal arteries were occluded for 105 minutes; severe renal depression was observed in this patient, who died from uremia.

EFFECT OF HYPOTHERMIA ON ISCHEMIC KIDNEY

Bogardus and associates[5] occluded the renal pedicle of dogs for 2 hours and reported a considerable rise in blood creatinine level. Chilling the canine kidney during 2 hours of renal ischemia resulted in a less marked rise in the creatinine level. Schloerb and his group[26] observed the effect of cooling to 3° C. Survival of dogs was apparent during moderate renal ischemia (2 to 4 hours). Steuber and associates[28] confirmed the protective effect of hypothermia on renal function and advocated temperatures in the 0 to 5° C. range. Mitchell and Woodruff[19] observed peripheral cortical infarcts in sheep kidneys when temperatures below 10° C. were obtained. However, at these levels kidney function was protected. Owens and co-workers[22] occluded the upper thoracic aorta of dogs after moderate hypothermia (23 to 26° C). Renal function was not compromised during 3 hours of ischemia. Couch and colleagues[8] excised dog kidneys and perfused them at 25° C. With simple diluents, urine production was maintained for 7 hours, though at slightly reduced levels. Recently Cassie and co-workers[6] perfused excised dog kidneys at normal temperatures. Observed functional impairment was comparable to reduced function found in the excised kidney perfused at 25° C.

EFFECT OF HYPOTHERMIA ON RENAL FUNCTION

Page and his group[23] reported a linear decrease in glomerular filtration rates and renal plasma flow during decrease in temperature. However, on rewarming of the dogs, renal function returned promptly to normal without evidence of residual damage. Hong[15] confirmed these same results in rats and squirrels. Moyer and associates[21] found a decrease in glomerular filtration rate and renal blood flow in 39 dogs at 27° C. Sodium excretion was not altered. Immediately after return to normothermia, renal function was 75 per cent of normal and return to normal levels was accomplished in 24 hours. Morales and his co-workers[20] treated 11 patients with hypothermia (30° C.). At lower temperatures glomerular filtration rate was reduced to 52 per cent; renal blood flow was 56 per cent of normal.

METHODS

This study was formulated to evaluate a stainless steel kidney cooler, compact in design and readily adaptable to patients of all age groups. An intrarenal temperature of 18° C. was preselected to determine the effect of 2 hours renal ischemia with this device* (Fig. 1).

Fifteen mongrel dogs which ranged in weight from 11 to 22.5 kilograms were di-

*Manufactured by The Garrett Corporation, Los Angeles, Calif.

vided into 4 groups. All dogs were anesthetized intravenously with pentobarbital sodium, after which laparotomy was performed. Bilateral ureterostomies in situ were performed. The ureters were not divided. Polyethylene catheters were passed from the midureter to the renal pelvis on each side. Urine collections were made from each kidney before and after each procedure. Renal function was measured by standard clearance techniques (creatinine and para-aminohippuric acid infusion). Group I consisted of control dogs (Table I). Experiments were carried out in Groups II, III, and IV. In these 3 groups, the left kidney was cooled to an intrarenal temperature of 16 to 20° C. The right kidney remained at normal body temperature and was used as a control. Temperatures were recorded by small thermocouples imbedded 1 inch into the renal cortex.

In Group II, renal arteries were occluded for ½ hour. After release of the bulldog clamp from the renal artery, urine collections were obtained at hourly intervals for the ensuing 6 hours. In Group III, renal arteries were occluded for 1 hour. The arteries were clamped for 2 hours in Group IV.

After mobilization of the left kidney, 2 stainless steel shells were placed around the kidney before clamping of the renal artery. An inlet from each half shell was connected in series with rubber tubing. The remaining inlet from each shell was connected to a reservoir which supplied the coolant (Fig. 2).

RESULTS

Effects of intravenous pentobarbital sodium anesthesia on renal function are given in Table I. The data include determinations of kidney function obtained from 3 dogs in the control group.

Fig. 3 represents an experiment which quite generally illustrates the events subsequent to renal ischemia for one-half hour. Five hours after hypothermia the glomerular filtration rate on the left returned to 18.5 ml. per minute, whereas in the right kidney it was 7 ml. per minute. Renal plasma flow followed the same pattern.

Table I. *The effect of intravenous pentobarbital sodium on renal function*

Dog No.	*Weight (Kg.)*	*Glomerular filtration rate (ml./min.)*		*Renal plasma flow (ml./min.)*	
		Left	*Right*	*Left*	*Right*
1	12.4	21	21	59	59
		20.7	22	57	56
2	17.9	30	31	66	69
3	22.1	38	36	90	95
		37	35	92	79

Fig. 2. Closed circuit path of coolant.

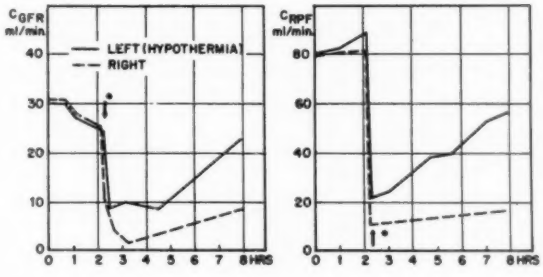

Fig. 3. Illustrative experiment from Group II. The effect of 18° C. hypothermia (*) on renal ischemia for one-half hour in a 13.1 kilogram dog.

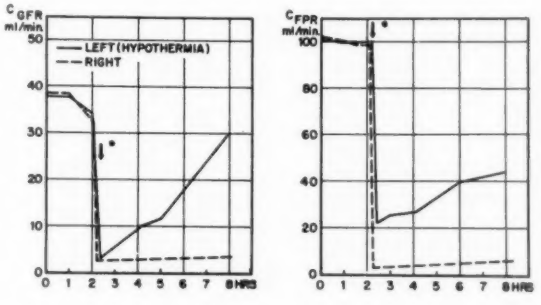

Fig. 4. Illustrative experiment from Group III. Effect of 18° C. hypothermia (*) on renal ischemia for 1 hour in a 15.5 kilogram dog.

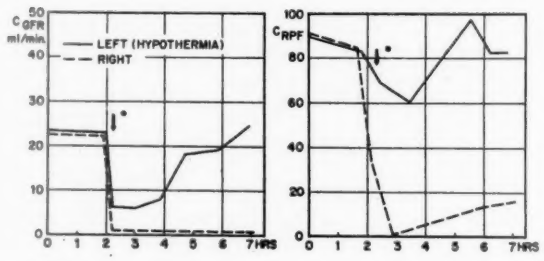

Fig. 5. Illustrative experiment from Group IV. Effect of 18° C. hypothermia (*) on renal ischemia for 2 hours in an 11.2 kilogram dog.

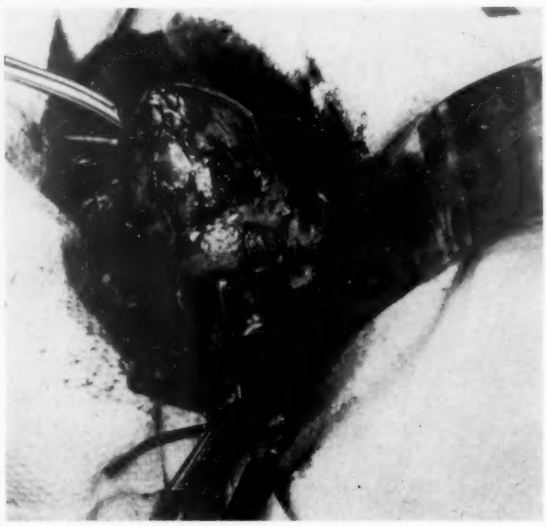

Fig. 6. Two quarter shells of the cooler in place on half of kidney prior to heminephrectomy.

Fig. 4 depicts the effects of hypothermia which are more marked 5 hours after the renal artery clamps are removed. Renal function in the right kidney remains depressed (less than 5 ml. per minute).

The events found after 2 hours of ischemia are plotted in Fig. 5. The differences observed are quite pronounced; return to normal on the hypothermic side is seen.

The kidney cooler has been employed in 6 clinical cases. Fig. 6 is a photograph of the cooler prior to heminephrectomy for a solitary calculus in the lower pole.

In Fig. 7 the apparatus is in position prior to a renal bivalving procedure. Temperatures of 12 to 18° C. were obtained in each instance. The renal artery was clamped 55 to 92 minutes in the 6 patients. An intravenous pyelogram obtained 5 days after renal bivalving for removal of a staghorn calculus showed prompt function.

Rate of cooling is graphically illustrated in Fig. 8. Kidney core and surface temperatures were monitored. Five minutes after occlusion of the renal artery, core temperature was 27° C., whereas surface temperature was 22° C. Within 15 minutes temperatures of 16 to 19° C. were obtained.

DISCUSSION

These findings add to evidence already available that regional kidney hypothermia protects renal function during ischemia. At temperatures of 18° C., 2 hours of renal ischemia is well tolerated by the experimental animal. In the 6 clinical cases hypothermia was tolerated without apparent loss of renal function. Heminephrectomies were performed with use of 2 mirror-image quarter shells which encased half of the kidney.

These studies give additional support to views previously expressed that regional kidney hypothermia is indicated in situations which demand prolonged clamping of the renal vessels or the adjacent aorta. Renal endarterectomies and bypass operations may be handled in this manner in the future. In many instances, renal function is at a reduced level prior to operation.

Because renal homotransplantations may soon be carried out on a wide scale, the cooler may prove useful during the interval before the donor kidney is transplanted.

Fig. 7. Cooling apparatus in position prior to renal bivalving procedure.

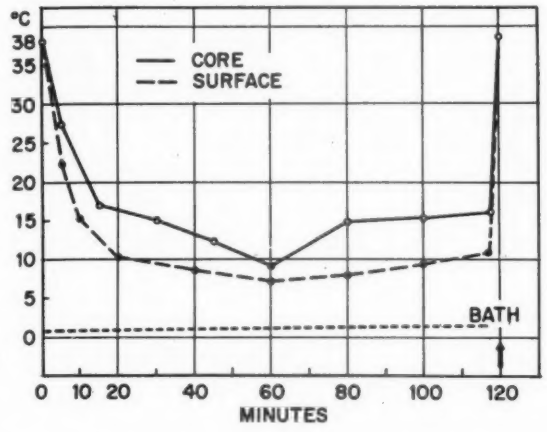

Fig. 8. Rate of cooling with regional kidney hypothermia.

Often, heminephrectomies or bivalving operations on the kidney require occlusion of the renal artery. Regional hypothermia can be beneficial in these instances.

SUMMARY

Previous reports have demonstrated depression of kidney function when renal ischemia was prolonged. This study presents additional evidence of a protective effect when regional renal hypothermia is utilized.

A device is described which rapidly attains hypothermic levels (12 to 18° C.) and maintains kidney core temperature at this lower level, thus allowing several hours of operating time.

The new method for cooling has been used in 6 clinical cases without apparent deleterious effects. Renal flow was temporarily interrupted in these patients for from 55 to 92 minutes.

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REFERENCES

1. Badenoch, A. W., and Darmady, E. M.: The effect of temporary occlusion of the renal artery in rabbits and its relationship to traumatic uremia, J. Path. & Bact. **59:** 79, 1947.
2. Bahnson, H. T.: Definitive treatment of saccular aneurysms of the aorta with excision of sac and aortic suture, Surg. Gynec. & Obst. **96:** 383, 1953.
3. Bahnson, H. T.: Treatment of abdominal aortic aneurysm by excision and replacement by homograft, Circulation **9:** 494, 1954.
4. Birkeland, S., Vogt, A., Krog, J., and Semb, C.: Renal circulatory occlusion and local cooling, J. Appl. Physiol. **14:** 227, 1959.
5. Bogardus, G. M., and Schlosser, R. J.: The influence of temperature upon ischemic renal damage, SURGERY **39:** 970, 1956.
6. Cassie, G. F., Couch, N. P., Dammin, G. J., and Murray, J. E.: Normothermic perfusion and replantation of the excised dog kidney, Surg. Gynec. & Obst. **109:** 721, 1959.
7. Cockett, A. T. K.: An experimental study: an apparatus for regional kidney hypothermia, S. Forum, Annual Meeting of the American College of Surgeons, San Francisco, Calif., 1960.
8. Couch, N. P., Cassie, G. F., and Murray, J. E.: Survival of the excised dog kidney perfused in a pump-oxygenator system, SURGERY **44:** 666, 1958.
9. Creech, O. Jr., De Bakey, M. E., Morris, G. C., and Moyer, H.: Experimental and clinical observations on the effects of renal ischemia, SURGERY **40:** 129, 1956.
10. De Bakey, M. E., Creech, O., Jr., and Morris, G. C.: Aneurysm of thoracoabdominal aorta involving celiac, superior mesenteric, and renal arteries. Report of four cases treated by resection and homograft replacement, Ann. Surg. **144:** 549, 1956.
11. Deterling, R. A., Jr., Nelson, E., Bhonslay, S., and Howland, L.: Study of basic physiologic changes associated with hypothermia, A. M. A. Arch. Surg. **70:** 87, 1955.
12. Ellis, F. H., Jr., Helden, R. A., and Hines, E. A., Jr.: Aneurysm of the abdominal aorta involving the right renal artery, Ann. Surg. **142:** 992, 1955.
13. Friedman, S. M., Johnson, R. L., and Friedman, C. L.: The pattern of recovery of renal function following renal artery occlusion in the dog, Circulation Res. **2:** 231, 1954.
14. Hamilton, P. B., Phillips, R. A., and Hiller, A.: Duration of renal ischemia required to produce uremia, Am. J. Physiol. **152:** 517, 1948.
15. Hong, Suk Ki: Renal function during hypothermia and hibernation, Am. J. Physiol. **188:** 137, 1957.
16. Kerr, W. K., Kyle, V. N., Keresteci, A. C., and Smythe, C. A.: Renal hypothermia, J. Urol. **84:** 236, 1960.
17. Koletsky, S.: Effects of temporary interruption of renal circulation in rats, A. M. A. Arch. Path. **58:** 592, 1954.

18. Mitchell, R. M.: Studies on renal transplantation in sheep, Australian & New Zealand J. Surg. **28:** 263, 1959.
19. Mitchell, R. M., and Woodruff, M. F. A.: The effects of local hypothermia in increasing tolerance of the kidney to ischemia, Transplantation Bull. **4: 15,** 1957.
20. Morales, P., Carbery, W., Morello, A., and Morales, G.: Alterations in renal function during hypothermia in man, Ann. Surg. **145:** 488, 1957.
21. Moyer, J. H., Morris, G., and De Bakey, M. E.: Hypothermia. I. Effect on renal hemodynamics and on excretion of water and electrolytes in dog and man, Ann. Surg. **145:** 26, 1957.
22. Owens, J. C., Prevedel, A. E., and Swan, H.: Prolonged experimental occlusion of thoracic aorta during hypothermia, A. M. A. Arch. Surg. **70:** 95, 1955.
23. Page, L. B.: Effects of hypothermia on renal function, Am. J. Physiol. **181:** 171, 1955.
24. Roof, B. S., Lauson, H. D., Bella, S. T., and Eder, H. A.: Recovery of glomerular and tubular function, including p-aminohippurate extraction, following two hours of renal artery occlusion in the dog, Am. J. Physiol. **166:** 666, 1951.
25. Scheibe, J. R., Giraldi, E., and Vermeulen, C. W.: The effect of temporary renal vascular occlusion on kidney function, SURGERY **25:** 724, 1949.
26. Schloerb, P. R., Waldorf, R. D., and Welsh, J. S.: The protective effect of kidney hypothermia on total renal ischemia, S. Forum **8:** 633, 1957.
27. Semb, C.: Partial resection of the kidney: anatomical, physiological and clinical aspects, Ann. Roy. Coll. Surg. **19:** 137, 1956.
28. Steuber, P. J., Jr., Kovacs, S., Koletsky, S., and Persky, L.: Regional hypothermia in acute renal ischemia, J. Urol. **79:** 793, 1958.

Studies in balanced hypothermic perfusion

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In the laboratory and on the cardiovascular service of the Children's Hospital, profound hypothermia is induced by the incorporation of a heat exchange mechanism in a siphon-drainage pump-oxygenator system.[2, 7] Prior to initiation of cardiopulmonary bypass, the temperature of the priming blood volume is reduced to 5° to 10° C. by recirculation through the heat exchanger for a 10-minute period. Commencement of perfusion with this precooled blood results in a rapid reduction of temperatures recorded from the heart, brain, liver, esophagus, and rectum. Cardiac asystole becomes evident within the first minute of cold perfusion which permits immediate cardiotomy.

During the cooling phase (at approximately 20° C.), a reduction in perfusion blood flow occurs secondary to increments in peripheral vascular resistance and blood viscosity. This physiologic decrease in total flow diminishes bronchial return to the arrested heart and facilitates visualization of many intracardiac defects. If more adequate exposure becomes a necessity, the combination of profound hypothermia and extracorporeal circulation permits periods of total circulatory arrest with interruption of the coronary arterial circulation alone.

Hypothermic perfusions of long duration (60 to 120 minutes) have been accomplished without difficulty in animals and in patients who weighed more than 10.0 kilograms.[3] However, in small animals (4.0 to 9.0 kilograms body weight), the usual methods of maintaining an equilibrium between venous return to the oxygenator and arterial outflow are not entirely satisfactory. In the experiments to be described, all perfusions were carried out with the oxygenator and venous reservoir mounted on a sensitive scale mechanism. This permitted an accurate quantitation of blood flow in and out of the animal, and eliminated complications due to hypervolemia.

The metabolic and hemodynamic studies also included in this investigation were (1) determination of changes in total body oxygen consumption which occur during cooling to 10° C. and throughout the rewarming phase and (2) evaluation of left ventricular work capacity after periods of total circulatory arrest (15 to 45 minutes in duration) at 10° C.

METHODS AND MATERIALS

Experimental procedure. Thirty-six mongrel dogs of either sex which weighed 4.0 to 18 kilograms were used. The animals were anesthetized intravenously with pentobarbital sodium, 30 mg. per kilogram, and intu-

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bated. Respirations were controlled with a Bennett automatic respirator. A polyethylene catheter was placed in the left femoral artery, and mean blood pressure measured by means of a Statham pressure transducer and recorded with a Sanborn direct writer. Cannulation of the left femoral vein was also carried out to permit the intravenous administration of heparin, an antiheparin compound (hexadimethrine bromide), and a muscle relaxant (succinylcholine chloride). Serial electrocardiograms were obtained in all animals and recorded with a Sanborn Viso-Cardiette.

Simultaneous myocardial, brain, hepatic, and muscle temperatures were measured with thermiocouples mounted on 22 gauge needles. The brain needle was inserted through a temporal burr hole created prior to thoracotomy. Individual thermistor probes were also placed in the midesophagus and rectum and connected to a multiple-channel telethermometer for recording purposes.

A bilateral anterior thoracotomy was performed in all animals. The pleura was entered through the fifth intercostal space. Sodium heparin (1 mg. per kilogram of body weight) was administered intravenously after completion of the thoracotomy. In preparation for bypass, cannulation of the superior and inferior venae cavae was carried out in addition to insertion of sump drains through the atria into the right and left ventricles. This provided the return of systemic venous blood, coronary sinus blood, and bronchial collateral flow to a siphon-drainage Gross model pump-oxygenator system. A gas mixture containing 98 per cent oxygen and 2 per cent carbon dioxide (at a flow rate of 6 L. per minute) was used routinely in the oxygenator. Oxygenated blood was pumped through a stainless steel cannula in the right femoral artery.

The cooling phase of each experiment was accomplished in an average of 24 minutes, at which time the brain temperature was reduced to 10° C. After an interval of total circulatory arrest (15 to 45 minutes), rewarming of the blood was begun by circulation of warm fluid (40° to 42° C.) through the heat exchanger. Electrical defibrillation of the ventricles was accomplished with ease when the cardiac temperature reached 30° C., and decannulation of the cavae was carried out at a rectal temperature of 32° to 35° C. The mean duration of the rewarming period was 40 minutes.

For purposes of obtaining an accurate balance of perfusion blood flow, the disc oxygenator, motor, and venous reservoir were mounted directly on a Toledo scale (model 4020).* The connecting plastic tubing was suspended from a single vertical post fixed to the pump chassis (Fig. 1). Standardization of the scale with weights (1.0 to 100 Gm.) before each experiment permitted determination of changes in extracorporeal blood volume in increments of 2.5 Gm. A "zero" balance of the system was obtained after priming of the pump-oxygenator system with blood (2,800 ml.), and coupling of the caval and arterial perfusion lines to the animal.

Metabolic determinations. The changes in oxygen utilization which occurred during the intervals of cooling and rewarming were quantitated in 24 of the 36 dogs (Group I). To permit calculation of the oxygen consumption at 37° C., arteriovenous blood samples were obtained in 6 animals prior to thoracotomy. Simultaneous cardiac output determinations were carried out with a Gilford cuvette densitometer and indocyanine green dye.[10] During the reduction of body temperature, additional arteriovenous specimens were drawn anaerobically from the aorta and inferior vena cava at intervals of 5° C. (using brain temperature as reference). Blood samples were procured in a similar fashion throughout the rewarming phase beginning 2 minutes after the onset of warm perfusion. The oxygen capacity and percentage saturation of all specimens were measured by a spectrophotometric method.[8]

In 5 of the 24 animals (Group I), a muscle relaxant was administered intravenously throughout rewarming. This eliminated the effects of shivering and spontaneous muscular activity upon the oxygen consumption.

*Toledo Scale Corporation, Brighton, Mass.

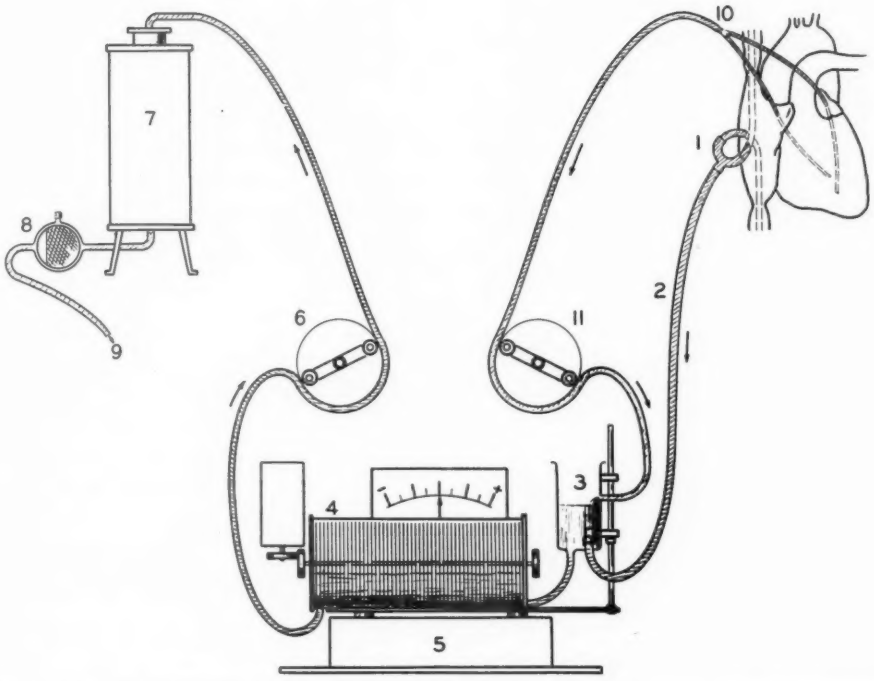

Fig. 1. Schematic representation of hypothermic perfusion with pump-oxygenator mounted on a Toledo scale. *1,* Y-tube with cannulas from both cavae. *2,* Caval drainage line. *3,* Venous reservoir. *4,* Kay-Cross oxygenator. *5,* Toledo scale. *6,* Pump returning blood to animal. *7,* Heat exchanger. *8,* Filter. *9,* Infusion into femoral artery. *10,* Coronary sinus and left ventricular sump drains. *11,* Pump for sump drains.

Evaluation of left ventricular function after varying periods of total circulatory arrest. In a separate group of 12 dogs (Group II), left ventricular stroke work (gram-meters) was calculated from the formula:

$$\text{left ventricular stroke work} = \frac{\text{stroke volume in cubic centimeters} \times \text{mean arterial pressure (cm. } H_2O\text{)} - \text{mean left atrial pressure (cm. } H_2O\text{)}}{100}$$

Left atrial pressure, mean arterial pressure, and cardiac rate (electrocardiogram) were monitored continuously on a 4 channel Poly-Viso recorder. The left atrial pressure was varied between 10 and 30 cm. H_2O by infusion of whole blood through a polyethylene cannula secured in the left auricular appendage. Cardiac output determinations (with indocyanine green dye, a constant-speed withdrawal pump, and a cuvette densitometer) were performed after stabilization of the atrial pressure. Left ventricular function curves were constructed from these data by plotting stroke work (gram-meters) against left atrial filling pressure.[9] A composite "normal" curve containing the mean stroke work data from 8 animals (37° C.) was used for comparison with the posthypothermic stroke work data. The latter values were obtained in dogs which survived total circulatory arrest for periods of 15 to 45 minutes at 10° C. (heart, brain, liver, and esophagus), and rewarmed to 35° to 37° C. During the interval of circulatory arrest, the application of cold saline solution to the epicardial surface of the heart was necessary to prevent spontaneous cardiac rewarming.

RESULTS

Balanced hypothermic perfusion. In 24 animals (Group I) utilized for the oxygen consumption study, the rapidity of cooling and rewarming was directly proportional to the existing blood flow and perfusion pressure (Figs. 2 and 3). Throughout the cooling phase (mean duration 24 minutes),

temperatures recorded in the esophagus, heart, brain, rectum, and muscle decreased at rates varying from 1.2° C. per minute to 0.6° C. per minute. These changes were associated with a decline in the average perfusion blood flow (70 ml. per kilogram per minute to 50 ml. per kilogram per minute) and mean arterial pressure (136 to 100 mm. Hg).

Rewarming required an average of 40 minutes. At the conclusion of this period, the rectal and brain temperatures were elevated to the range of 32° to 35° C. Termination of the warm perfusion (40° C.) prior to this time resulted in a hazardous downward drift of cardiac, brain, liver, and esophageal temperatures toward the level of the existing rectal temperature.

An accurate balance of the extracorporeal blood volume (venous return and arterial outflow) was maintained by observation of the "zero" indicator on the scale chart. When variations in the rate of perfusion were noted, compensation was accomplished by adjustment of the speed (revolutions per minute) of the rotary arterial pump. This

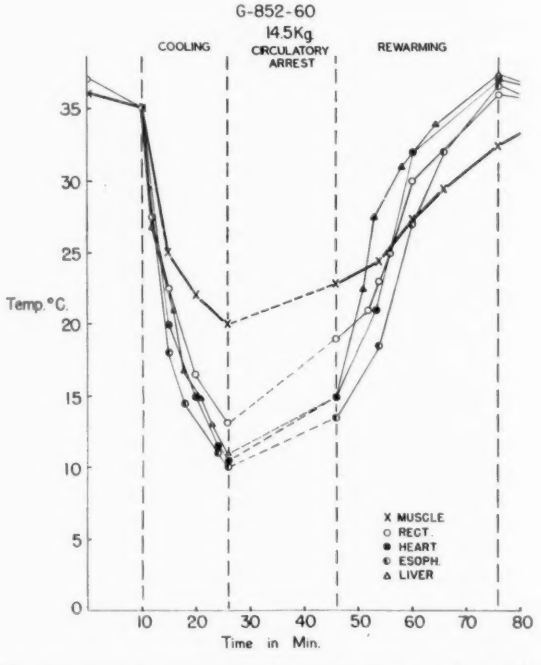

Fig. 2. Graphic presentation of changes in body temperature during cooling, a 20-minute period of total circulatory arrest, and throughout the rewarming phase. An upward drift in temperature occurs during interruption of perfusion.

system of perfusion control proved to be of maximal value in 5 small animals of Group I which weighed 4.0 to 9.0 kilograms (Table I). In these dogs, perfusion flows during cooling ranged from a maximum of 60 ml. per kilogram per minute to a minimum of 39 ml. per kilogram per minute, and increased slightly during the return to normothermia (41 to 68 ml. per kilogram per minute). The mean duration of each phase was similar to that recorded for animals which weighed over 10.0 kilogram (Fig. 3).

The 5 puppies in Group I survived for intervals of 3 to 14 days, and will be included in a larger series of small animal perfusions to be reported separately in a more comprehensive study. The remaining 19 larger dogs were sacrificed at the conclusion of rewarming to provide a source of donor blood.

Oxygen consumption during profound hypothermia. The effects of temperature and a 40-minute period of total circulatory arrest upon oxygen consumption are graphically presented in Fig. 4. The mean uptake of oxygen by 19 of 24 dogs (Group I) was found to be 5.0 c.c. per kilogram body weight per minute at 37° C., 3.0 ± 0.59* c.c. per kilogram per minute at 30° C., 1.8 ± 0.28* c.c. per kilogram per minute at 20° C., and 0.8 ± 0.16* c.c. per kilogram per minute at 10° C. The perfusion flow rate in all animals during cooling ranged between 50 and 70 ml. per kilogram per minute.

A 5 degree upward drift in temperature (using brain temperature as reference) occurred during the 40-minute interval of circulatory arrest. Therefore, active rewarming was begun at 15° C. The data collected at intervals of 5° C. disclosed a mean oxygen utilization of 3.4 c.c. per kilogram body weight per minute at 15° C., 3.9 c.c. per kilogram per minute at 20° C., 3.9 c.c. per kilogram per minute at 25° C., 4.6 c.c. per kilogram per minute at 30° C., and 4.7 c.c. per kilogram per minute at 37° C. In 5 additional animals (Group I), succinylcholine chloride was administered intravenously throughout rewarming. The mean

*Standard error of the mean.

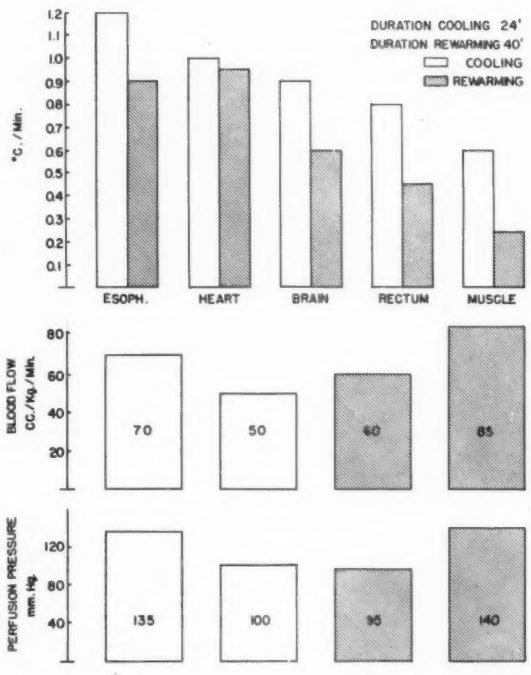

Fig. 3. Rapid rates of temperature change are noted in the esophagus, heart, and brain throughout cooling and rewarming, while temperature from the rectum and muscle mass lag behind. During the cooling phase, an increase in blood viscosity is the predominant factor responsible for the decrease in blood flow and mean perfusion pressure. All data represent mean values from 10 animal experiments.

oxygen uptake in these animals was 4.0 c.c. per kilogram per minute at 20° C., 4.0 c.c. per kilogram per minute at 25° C., and 4.1 c.c. per kilogram per minute at 37° C.

Left ventricular function studies. Each animal of Group II was subjected to a single period of total circulatory arrest (15, 30, or 45 minutes in duration) at 10° C. Post-arrest left ventricular function studies were performed 30 minutes after termination of rewarming, when the rectal, brain, and cardiac temperatures were in the range of 35° to 37° C. Representative curves before and after interruption of the circulation for the maximum period (45 minutes) are presented in Fig. 5. They demonstrate a mean stroke work capacity equivalent to 90 per cent of the control values.

DISCUSSION

Profound hypothermia in conjunction with cardiopulmonary bypass facilitates the surgical correction of many complex cardiac defects. The method used in this center incorporates a heat exchanger with a siphon-drainage pump-oxygenator system, and includes the initiation of perfusion with a precooled (5° to 10° C.) extracorporeal blood volume. This preliminary step accelerates the rate of total body cooling and produces a precipitous reduction in myocardial temperature. Cessation of rhythmic cardiac contractions occurs during the first minute of perfusion which permits prompt cardiotomy.

The versatility of this method is evident from the fact that several of the more common congenital defects (tetralogy of Fallot and ventricular septal defect) can be repaired in the cold arrested heart during continuous perfusion. In other cases (valvular or supravalvular aortic stenosis, for example), interruption of the coronary circulation alone or total circulatory arrest can be employed to enhance intracardiac visibility.

Table I. *Balanced hypothermic perfusion in 5 small animals (4.0 to 9.0 kilograms)*

		Perfusion flow (ml./min.)				*Perfusion pressure (mm. Hg)*				*Lowest temperatures (C.)*		
		Cooling		*Rewarming*		*Cooling*		*Rewarming*		*Prior to circulatory arrest*		
Animal No.	*Weight (Kg.)*	*Maximum*	*Minimum*	*Maximum*	*Minimum*	*Maximum*	*Minimum*	*Maximum*	*Minimum*	*Rectum*	*Esophagus*	*Heart*
G-216-60	9.0	600	450	600	450	135	125	145	120	14	9	9
G-678-60	8.0	450	300	500	300	145	70	130	100	17	9	9
G-M55-60	6.5	360	240	600	300	100	70	110	80	17	11	10
G-M136-60	4.5	300	150	360	180	100	75	150	75	15	10	10
G-M134-60	4.0	240	150	300	180	140	85	75	130	13	13	12

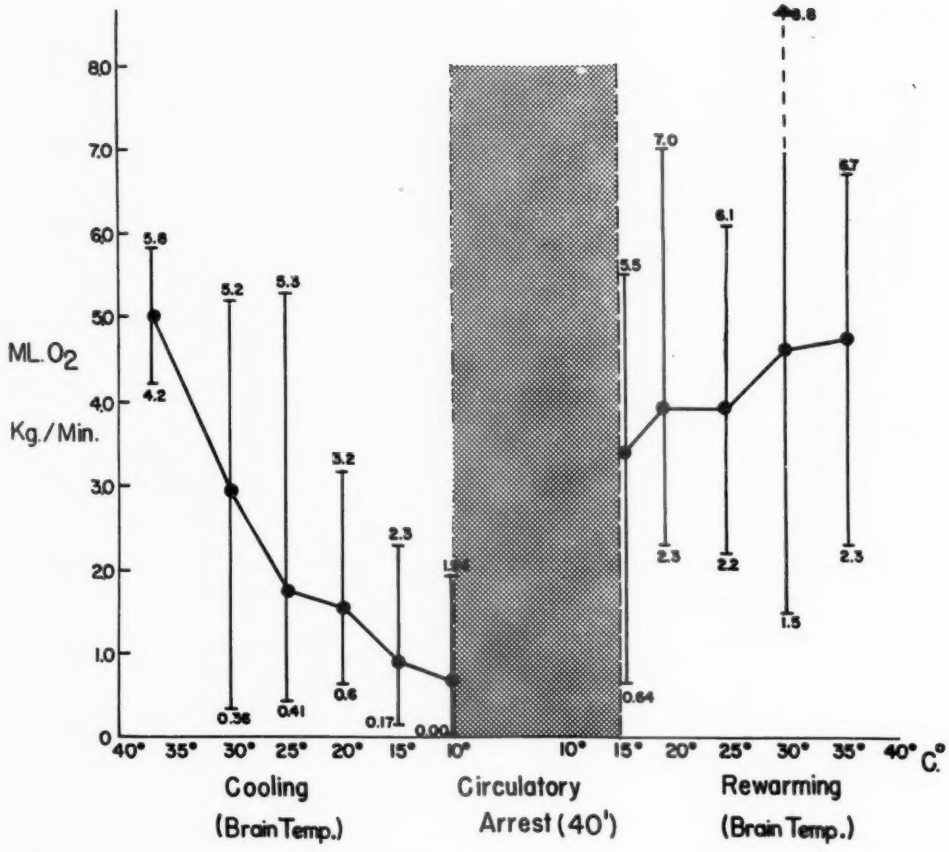

Fig. 4. Mean oxygen utilization data (and range of the mean) from the animals of Group I during the phases of cooling and rewarming. The rewarming values indicate the existence of an oxygen debt, incurred mainly within the interval of total circulatory arrest.

A comparison seems warranted between this technique for the production of profound hypothermia and that developed by Drew.[5] The most salient feature of the latter method is the use of autologous lung as the oxygenator. Although a more physiologic gas exchange may be accomplished in this manner, certain disadvantages appear evident. First, 2 separate propulsion circuits are required to pump venous blood through the lungs and to return oxygenated blood to the arterial tree. Second, the necessity of maintaining pulmonary blood flow during cooling delays the beginning of cardiotomy (20 to 30 minutes). Third, pulmonary perfusion under sufficient pressure to overcome varying degrees of vascular obstruction (pulmonary hypertension) may result in irreversible pulmonary parenchymal damage. Fourth, cardiac operations may be carried out only during periods of total circulatory arrest, an unnecessary risk in many instances.

The establishment of an equilibrium between venous return to the oxygenator and arterial outflow to the experimental animal is essential for a successful bypass. Although this is accomplished in the majority of instances, present techniques do not eliminate transient errors in the balance of perfusion flow (100 to 300 ml.). In the immediate postperfusion period, discrepancies of this magnitude are tolerated by dogs with an initial blood volume of 1,000 ml. or greater. However, errors of similar degree in smaller animals (blood volumes of 500 ml. or less) result in severe hypervolemia and right heart failure.

The quantitative type of hypothermic perfusion utilized in these experiments offers 1 solution to the problem. In this method, an oxygenator and venous reservoir are mounted on 1 side of a double-pan Toledo

scale. After priming with donor blood, all of the apparatus is counterbalanced with approximately 30 Kg. of standard weights. Thereafter, equilibration between caval return and arterial outflow (measured in grams) is maintained by varying the speed (r.p.m.) of a rotary arterial pump. Throughout each perfusion, the single objective of the pump operator is to maintain the scale indicator arm on the "zero" mark. Accomplishment of this objective guarantees an accurate, balanced perfusion.

The change in left ventricular function after periods of total circulatory arrest (10° C.) permits a critical evaluation of the protective effect of reduced temperature upon the myocardium.[4] The data obtained from the animals of Group II demonstrate a 10 per cent reduction in work capacity after cessation of blood flow for a maximum of 45 minutes. No reduction was noted after total arrest for intervals of 15 and 30 minutes. These results are in general agreement with those given in another published report and indicate that a cardiac temperature of 10° C. provides a substantial degree of protection from the degenerative effects of hypoxia.[6]

In vitro studies of tissue homogenates and oxidizing enzyme systems (cytochrome oxidases) indicate that neither oxygen uptake nor electron transfer are limited at temperatures near 0° C.[1] Therefore, the decrease in oxygen consumption which accompanies a reduction in body temperature is dictated only by a lessened demand for oxygen in each metabolically active cell.

Quantitation of this reduction in utilization is presented in the data obtained from the animals of Group I. A 40 per cent decrease (from the control value, 37° C.) is evident at 30° C. and this progresses to 64 per cent at 20° C. and 84 per cent at 10° C. These data tend to confirm the impression that no physiologic end point exists above 0° C. at which the demand for oxygen completely ceases.

The mean oxygen uptake during the rewarming phase (after 40 minutes of total circulatory arrest) indicates the occurrence of an oxygen debt. Substantiation of this fact is provided by the presence of similar increases in utilization (at 15°, 20°, and 25° C.) noted in the animals which received succinylcholine. Since the oxygen uptake at the end of rewarming (37° C.) never exceeds the precooling control values, the existing debt must be satisfied during the period of warm perfusion.

SUMMARY

1. A method of balanced hypothermic perfusion is described which permits quantitation of changes in total blood flow in increments as small as 2.5 Gm.

2. The practicality of this technique is demonstrated for cardiopulmonary bypass in small animals (4.0 to 9.0 kilograms body weight).

3. The total body oxygen consumption was determined during cooling to 10° C., after a 40-minute period of total circulatory arrest, and throughout rewarming.

4. An oxygen debt was detected during the rewarming phase of all experiments.

5. The administration of succinylcholine

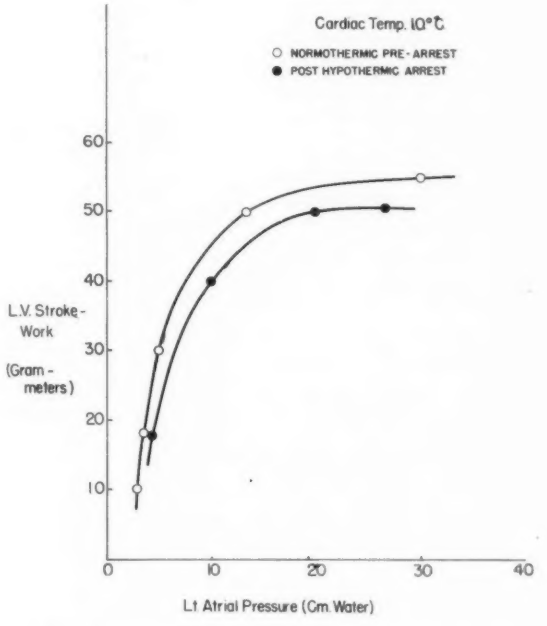

Fig. 5. Comparison of a left ventricular function curve after hypothermic arrest with precooling values. The study was performed 30 minutes after rewarming and indicated a slight decrease in stroke work ability.

chloride throughout this period failed to alter the dimensions of the debt.

6. Since the oxygen utilization during return to normothermia never exceeded the precooling (control) rate, a rapid satisfaction of this deficiency must have occurred.

7. Evaluation of left ventricular stroke work was performed before and after varying periods of total circulatory arrest at 10° C. The postarrest studies (carried out 30 minutes after rewarming) disclosed a 10 per cent reduction in left ventricular function after 45 minutes of cardiac ischemia.

REFERENCES

1. Adolph, E. F.: Effects of low body temperature on tissue oxygen utilization. The physiology of induced hypothermia, National Research Council, Pub. No. 451, p. 44, 1956.
2. Bernhard, W. F., and Gross, R. E.: Extracorporeal circulation and profound hypothermia. A new surgical technique, Proc. New England Cardiovasc. Soc., vol. XIX, 1960-1961.
3. Bernhard, W. F., Schwarz, H. F., and Mallick, N. P.: Intermittent cold coronary perfusion as an adjunct to open heart surgery, Surg. Gynec. & Obst. **111:** 744, 1960.
4. Bernhard, W. F., Schwarz, H. F., and Mallick, N. P.: Profound hypothermia as an adjunct to cardiovascular surgery, J. Thoracic Surg. **42:** 263, 1961.
5. Drew, C. E., Keen, G., and Benazon, D. B.: Profound hypothermia, Lancet **1:** 745, 1959.
6. Greenberg, J. J., Edmunds, H. L., and Brown, R. B.: Myocardial metabolism and postarrest function in the cold and chemically arrested heart, SURGERY **48:** 31, 1960.
7. Gross, R. E., Sauvage, L. R., Pontius, R. G., and Watkins, E.: Experimental and clinical studies of siphon-filling disc oxygenator system for complete cardiopulmonary by-pass, Ann. Surg. **151:** 285, 1960.
9. Stainby, W. W., Fales, J. T., and Lilienthal, J. L.: A rapid spectrophotometric method for determining oxygen content of dog's blood, J. Appl. Physiol. **7:** 577, 1955.
8. Sarnoff, S. J., and Berglund, E.: Ventricular function. I. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog, Circulation **9:** 706, 1954.
10. Wood, E. H., Swan, H. J., and Helmholz, H. F.: Symposium on diagnostic applications of indicator-dilution techniques, Proc. Staff Meet. Mayo Clin. **32:** 463, 1957.

The influence of hypothermia on experimental bacteremia in dogs

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General hypothermia alters many physiologic mechanisms, but its influence on the response to infection and bacteremia at 30° C. (86° F.) is not clearly understood. Recently Allen[1] reported on a small group of patients thought to be in profound septic shock who improved promptly after the induction of hypothermia. It is difficult to define the sites at which hypothermia may have exerted its beneficial effects, but it seems probable that clinical improvement attended the use of hypothermia. A search of the literature yielded few reports on this subject and much of the evidence was conflicting.[1, 4, 5, 10, 11] In studying this problem, we noted that in hypothermic dogs the removal of bacteria from the blood was slower than normal. This report describes a controlled series of experiments intended to test this initial observation.

METHOD

A pair of dogs of approximately equal weight was studied in each experiment. Each animal was used in 1 experiment only. After intravenous induction of anesthesia with pentobarbital sodium, 25 mg. per kilogram, 1 member of the pair was immersed in ice water until the temperature in the distal esophagus was 33.5° C. The dog was then removed and dried, and an endotracheal tube was inserted to which a respirator was connected. When the temperature had stabilized between 29° and 31° C., the pulse rate was found to have fallen from the normal rate of over 160 beats per minute to 80 beats per minute or less. Under sterile conditions a polyethylene catheter was inserted through the femoral vein into the iliac vein. Through this catheter a control specimen for blood culture was taken. Equal aliquots of *E. coli* in saline suspension (50 to 200 million colonies per milliliter) were injected into the 2 animals and the catheter then replaced with a longer one which extended into the inferior vena cava.

The infecting dose varied from experiment to experiment, but each animal of a pair received a volume of a uniformly dispersed suspension proportional to its body weight. The patency of the catheter was maintained by a continuous infusion of 5 per cent dextrose in distilled water at 60 drops per minute. Blood samples were taken in acid citrate dextrose solution at 10-minute intervals for 40 minutes after injection. Pour plates, with appropriate dilutions, were made immediately. In Experiments 1, 7, and 8 more frequent specimens were taken. The plates were incubated at 37° C. and inspected on the next day. Colony counts were made over a lighted grid. After the last specimen had been obtained the catheter was removed, the vein ligated, and the wound closed. The hypothermic dog was rewarmed with a Therm-O-Rite blanket until the esophageal temperature was 34.5° C. and spontaneous respirations were adequate. The rewarming process required 1½ to 2 hours. The animals were returned to their

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cages and observed. No antibiotics were given. Food and water were made available.

RESULTS

Bacteremia. In 7 out of 8 experiments the hypothermic dog showed a delay in clearing the blood of injected bacteria as compared to the clearing in the normothermic control dog (Fig. 1). This delay was most evident at 10 minutes, but the same tendency was present at 20 minutes. After 30 and 40 minutes, the colony counts were approximately equal. The statistical significance of this early variation is indicated by a p value between 0.03 and 0.04.

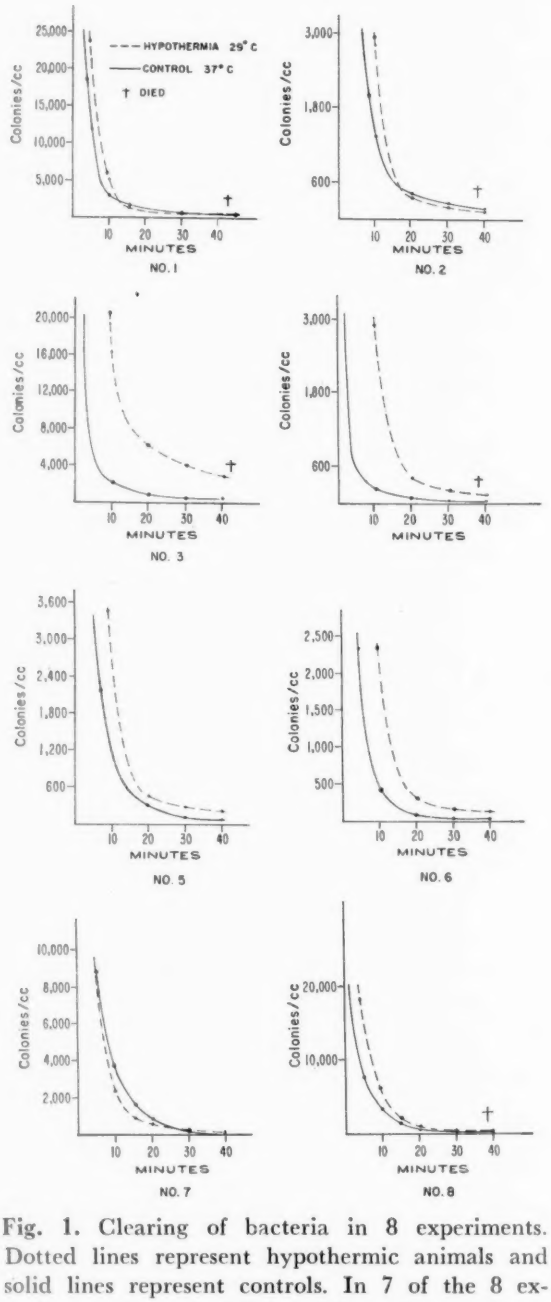

Fig. 1. Clearing of bacteria in 8 experiments. Dotted lines represent hypothermic animals and solid lines represent controls. In 7 of the 8 experiments removal of injected bacteria was slower in the hypothermic dog than in the control. In Experiments 1, 2, 3, 4, and 8, the hypothermic dog died after rewarming. There were no deaths among the controls.

Mortality rate. Five of the 8 hypothermic dogs died after rewarming, whereas there were no deaths among the control animals. There were no late deaths in either group. In 1 experiment it was possible to perform an autopsy immediately after death, 5 hours after the experiment had been completed. Blood taken from the heart in this animal was sterile on culture. All viscera were found to be markedly congested and sections of the liver, spleen, kidney, and lung did not show evidence of inflammation or bacteria. The p value for deaths lies between 0.01 and 0.02.

COMMENT

In 1943 Muschenheim,[9] using Goodner's[7, 8] standard pneumococcic dermal infection in rabbits, found that nonfatal infections became fatal if hypothermia were used. On the other hand, Wotkyns and associates,[11] in 1956, studied experimental pneumococcic peritonitis in mice and found that survival was prolonged when a fatal dose was given while the animals were hypothermic. Moreover, they found that with smaller doses the survival rates were improved by hypothermia. Also in 1956, Fedor and associates[5] induced a coliform bacteremia in dogs and found that the number of bacteria in the peripheral blood was reduced by 99 per cent 6 hours later. The cultures remained positive during the 12 to 18 hour periods of hypothermia, but became negative with rewarming. It is of interest that 7 out of their 13 animals died, a mortality rate consistent with our observations. Frank and colleagues[6] found a high mortality rate when bacteremia was induced in dogs under hemorrhagic shock, but when hypothermia was used, the mortality rate was reduced. However, Sanders and co-workers[10]

repeated the work of Muschenheim[9] and confirmed the observation that hypothermia increased the mortality rate in pneumococcic infections in rabbits.

The present study demonstrated that in a hypothermic dog the blood stream is not cleared of injected viable bacteria as quickly as in a normothermic dog. Although the mechanism of delay has not been defined, the removal of particulate matter from the blood is known to occur in the reticuloendothelial system, principally the liver.[2] In hypothermia the blood flow to the liver is reduced[3] along with a decrease in cardiac output. Phagocytic activity was not studied in this experiment, but there is conflicting experimental evidence[4] on the in vivo influence of hypothermia on this function.

The second point of interest is the high mortality rate in the hypothermic dogs and absence of deaths in the control group. In Fedor's[4] experiment as stated previously, 7 out of 13 hypothermic dogs with induced bacteremia died. In the 5 deaths among our animals, 4 occurred between the sixth and twentieth hours after rewarming. Postmortem heart blood culture and histologic examination, performed in 1 animal, failed to show evidence of residual viable organisms. This finding may indicate that susceptibility to the lethal effect of gram-negative endotoxins is increased in the hypothermic state.

A direct comparison of our results with those of others is made difficult by the differences in experimental design. Despite the variations in animals used, the type and dosage of organism, and the duration of hypothermia, the evidence indicates an impairment of resistance due to hypothermia. Further investigation will be necessary to clarify the effects of hypothermia on the humoral and cellular responses to infection.

SUMMARY

In order to test the effect of hypothermia on the removal of gram-negative bacteria from the blood, a series of controlled experiments was made in dogs. Blood cultures obtained at intervals of up to 40 minutes demonstrated a delay in removal of the bacteria by the hypothermic dog as compared with a normothermic control animal. In the hypothermic groups there was a 62 per cent mortality rate. No deaths occurred among the controls. It is concluded that under the conditions of these experiments hypothermic dogs have an impaired ability to cope with bacteria injected into the blood stream.

REFERENCES

1. Allen, J. M., Estes, J. T., and Mansburger, A. R.: The use of hypothermia in septic shock, Am. Surgeon **26:** 1, 1960.
2. Beeson, P. B., Brannon, E. S., and Warren, J. V.: Observations on the sites of removal of bacteria from the blood in patients with bacterial endocarditis, J. Exper. Med. **81:** 9, 1945.
3. Dripps, R.: The physiology of hypothermia, National Research Council, Pub. No. 451, 1956.
4. Fedor, E. J., Fisher, B., and Fisher, E. R.: Observations on the bacterial defense mechanisms during hypothermia, SURGERY **43:** 807, 1958.
5. Fedor, E. J., Fisher, E. R., Lee, S. H., Weitzel, W. K., and Fisher, B.: The effect of hypothermia upon induced bacteremia, Proc. Soc. Exper. Biol. & Med. **93:** 510, 1956.
6. Frank, E. D., Davidoff, D., Friedman, E. W., and Fine, J.: Host resistance to bacteremia in hemorrhagic shock. IV. Effect of hypothermia on intravenously injected bacteria, Proc. Soc. Exper. Biol. & Med. **91:** 188, 1956.
7. Goodner, K.: The effect of pneumococcic autolysates upon pneumococcic dermal infection in the rabbit, J. Exper. Med. **58:** 153, 1933.
8. Goodner, K.: Experimental intradermal pneumococcic infection in rabbits, J. Exper. Med. **48:** 1, 413, 1928.
9. Muschenheim, C., Duerachner, D. R., Hardy, J. D., and Stoll, A. M.: Hypothermia in experimental infections, J. Infect. Dis. **72:** 187, 1943.
10. Sanders, F., Crawford, E. S., and De Bakey, M. E.: Effects of hypothermia on experimental intracutaneous pneumococcic infection in rabbits, S. Forum **8:** 92, 1957.
11. Wotkyns, R. S., Hirose, H., and Eiseman, B.: Prolonged hypothermia in experimental pneumococcic peritonitis, S. Forum **8:** 89, 1957.

Reconstruction after total gastrectomy

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Although indications for total gastrectomy in patients with cancer of the stomach have been fairly well established and the immediate postoperative mortality rate for this operation has been reduced to acceptable levels, an important problem remains, namely, the type of reconstruction of the alimentary tract which is to be utilized. This consideration is important because it is well known that total excision of the stomach is frequently followed by a complex of symptoms known as the "agastric syndrome" which consists of bilious regurgitation, esophagitis, anemia, steatorrhea, and the dumping syndrome. Since a number of these sequelae may be due to technical factors, many improvements in technique have been suggested to avoid them.

To the more simple methods of reconstruction, such as the Roux Y or end-to-side esophagojejunostomy combined with a side-to-side Braun anastomosis, have been added other more complex methods of reconstruction. The aim of the latter is to create an interposed artificial stomach with a segment of either the small or large intestine. For example, Hunt[3] improved the Roux Y method by constructing a pouch from the upper part of the mobilized jejunal loop by a side-to-side anastomosis. Nakayama[8] utilized a loop of jejunum joined to itself by an end-to-side anastomosis which he interposed between esophagus and duodenum. Engel,[1] Tomoda,[11] Longmire,[5, 6] and others have interposed the small intestine in various ways. Hunnicult,[2] Lee,[4] and McClone[7] have utilized the cecum for this purpose, while State[10] utilized the transverse colon as a substitute stomach pouch.

During the decade from 1951 through 1960 we have had the opportunity to perform 79 total gastrectomies for gastric cancer. In the first 14 of the patients a simple technique was employed for reconstruction of the alimentary tract; in 7 the Roux Y anastomosis was performed, and in 7 an end-to-side esophagojejunostomy with a Braun anastomosis was carried out. In the next 23 patients the method of Nakayama was utilized. In the final 42 patients of this series, the technique to be described was carried out. This reconstruction consists of transection of the jejunum 7 to 10 cm. distal to the ligament of Treitz. The free end of jejunum is folded over and joined end-to-side to itself. To the loop thus formed the esophagus is anastomosed above, and distal to the loop the transected duodenum is anastomosed to the side of jejunum. Finally, an end-to-side anastomosis between the cut proximal end of the jejunum and the mobilized segment is performed (Fig. 1).

CLINICAL MATERIAL

During the decade from 1951 through 1960, 221 patients were operated upon in

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this clinic for gastric cancer. Table I shows the type of operation performed and the immediate postoperative mortality rate.

The type of operation to be employed was decided upon only after consideration of the patient's general condition and age, the situation of the tumor, and the presence or absence of metastases. Unresectable tumors were considered to be those in which diffuse spread or multiple metastases were present. Gastroenterostomy was performed for aged and debilitated patients with large pyloric tumors, usually with metastases in the liver and elsewhere. Wide subtotal gastrectomy was performed for localized pyloric tumor and was always combined with resection of the greater omentum. In a small number of patients this was a palliative procedure. Total gastrectomy was utilized for patients with cancer of the body or cardia or for those with very large tumors in the pylorus with metastases to the local lymph nodes. In Table II is shown the location of tumors for which total gastrectomy was performed.

Usually a midline incision was used which extended from the xiphoid process to a few centimeters below the umbilicus. This proved to be sufficient for any tumor of the body or pylorus. However, for cancers in the cardiac region a thoracoabdominal incision was utilized.

Table I. *Type of operation and mortality rate*

Type of operation	*No. of cases*	*Deaths*	*Mortality rates (%)*
Unresectable tumor	53	2	3.8
Gastroenterostomy	28	3	10.7
Subtotal gastrectomy	61	16	26.2
Total gastrectomy	79	10	12.6
Totals	221	31	14.03

Table II. *Location of tumors*

Situation of tumor	*No. of cases*
Cardiac region	11
Body of the stomach	42
Pylorus	26
Total	79

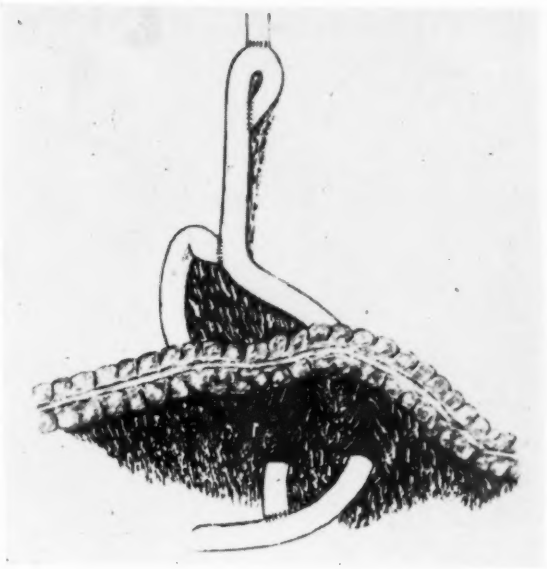

Fig. 1

Extent of the operation depended upon the findings at the time of laparotomy. If it was decided to perform a total gastrectomy, the lower 2 to 3 cm. of esophagus, the stomach and first part of the duodenum, the omenta, the tail of the pancreas, and the spleen were included in the resection. On 4 occasions we have resected the left lobe of the liver and in another 3 patients the operation was combined with resection of the transverse colon for spread of the tumor. Follow-up of patients has shown that resection of the left lobe of the liver was well tolerated, whereas results were less gratifying when resection of the transverse colon was added to the operation of total gastrectomy.

MORTALITY RATES

Table I shows the immediate postoperative mortality rates encountered. Twenty six and seven-tenths per cent of 61 patients who were treated by subtotal gastrectomy died, whereas 10 of 79 (12.6 per cent) patients treated by total gastrectomy died. The higher mortality rate encountered after subtotal gastrectomy is probably explicable by the fact that in many of the patients this operation was a palliative procedure.

In Table III are shown the mortality rates encountered after the various types of reconstruction utilized after total gastrectomy.

Fig. 2

Both patients who died after simple esophagoenterostomy Roux Y died because of disruption of the anastomosis followed by peritonitis. This complication was also responsible for 1 of the 2 deaths of patients operated upon by the Nakayama technique. In this instance peritonitis was caused by rupture of the end-to-end anastomosis of the mobilized distal end of the jejunum to the duodenum. The second death in this group was that of a patient with a cancer of the cardia for which a thoracoabdominal incision had been used. Six patients of a total of 42 operated upon by the technique described herein died. One died from irreversible postoperative shock, 2 from uremia, 1 from staphylococcal enterocolitis, and 2 from pneumonia. In 2 of the patients resection of the transverse colon which had been infiltrated by tumor was combined with total gastrectomy. Five of the 42 patients treated by this technique had carcinoma of the cardia which was removed with use of a thoracoabdominal incision. Four of the patients had neoplastic infiltration of the left lobe of the liver and another 3 had infiltration extended to the transverse colon. It is obvious that all the latter patients were operated upon in advanced stages of their disease. However, none of the deaths in the series were due to disruption of the anastomoses.

SURVIVAL RATES

Of the total of 69 patients who underwent a total gastrectomy and survived the operation, 12 died within 1 year, 7 died before the end of the second year, and 16 died before the end of the third year. Two patients are still alive 7 years, 2 are alive 5 years, and 6 are alive 3 years after the operative procedure. Fifteen patients are alive and well 1 year after the operation. The fate of the remaining 9 patients is unknown because they have been lost to follow-up.

DISCUSSION

Comparison of the results with the method described in 42 patients with cancer of the stomach with results of other methods which we have utilized in the past led us to conclude that this method has certain advantages over the other techniques. There have been no deaths from peritonitis due to disruption of an anastomosis and this, we believe, is due to the fact that the technique offers a double isoperistaltic outlet for food to the jejunum. The majority of food appears to pass through the duodenum. This has been verified by postoperative radiographs (Figs. 2 and 3).

Necrosis of the jejunal loop appears to be avoided in that a completely isolated loop is not utilized to join esophagus to duodenum.

Table III. *Technique of total gastrectomy and mortality rate*

Method used	*No. of cases*	*Deaths*	*Mortality rates (%)*
Simple technique	14	2	14.3
Nakayama's method	23	2	8.7
Our method	42	6	14.3

Fig. 3

In none of the patients treated by this technique was regurgitation of bile noted, whereas in 5 patients operated upon by other methods this distressing symptom was encountered and 3 of them developed severe esophagitis.

SUMMARY

1. Experiences with operative treatment of gastric cancer by total gastrectomy in 79 patients are reported.

2. A new technique for reconstruction of the alimentary tract after total gastrectomy is described.

REFERENCES

1. Engel, G. C.: The creation of a gastric pouch following total gastrectomy, SURGERY **17:** 512, 1945.
2. Hunnicult, A. J.: Replacing stomach after total gastrectomy with right ileocolon, A. M. A. Arch. Surg. **65:** 1, 1952.
3. Hunt, C. J.: Construction of food pouch from segment of jejunum as substitute for stomach in total gastrectomy, A. M. A. Arch. Surg. **64:** 601, 1952.
4. Lee, M.: Transplantation of a colon segment as a gastric reservoir after total gastrectomy, Surg. Gynec. & Obst. **92:** 456, 1951.
5. Longmire, W. P., Jr.: Total gastrectomy for carcinoma of the stomach, Surg. Gynec. & Obst. **84:** 21, 1947.
6. Longmire, W. P., Jr., and Beel, J. M.: Construction of a substitute gastric reservoir following total gastrectomy, Ann. Surg. **135:** 637, 1952.
7. McClone, F. B.: Total gastrectomy with replacement of stomach by ileocolic segment, J. A. M. A. **151:** 622, 1953.
8. Nakayama, K.: Evaluation of the various operative methods for total gastrectomy, SURGERY **40:** 488, 1956.
9. Paulson, M. H.: Hematological alteration after total gastrectomy, J. A. M. A. **156:** 1956, 1954.
10. State, D., Barkley, T. H. C., and Kelly, W. D.: Total gastrectomy with utilization of a segment of transverse colon to replace the excised stomach, Ann. Surg. **134:** 1035, 1951.
11. Tomoda, M.: Über den Stoffwechsel nach totalen Magenexstirpation, Chirurg. **23:** 545, 1952.

Prolonged functional survival of a secondary renal homotransplant in the dog

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Since Medawar[15] first convincingly demonstrated the occurrence of accelerated rejection in secondary skin transplant, it has been generally accepted that all types of secondary grafts will endure for shorter periods of time than the corresponding primary grafts, provided that the time interval between the implantation of the two is not too great.

In our laboratories, primary renal homografts in mongrel dogs were shown to have an average functional survival of 5.9 days, with a range of 2 to 14 days.[10] Dempster[6] reported a functional period of 4.4 days (range 1 to 10 days) in purebred greyhounds. The secondary transplants reported by Dempster[6] were performed 5 to 18 days after the primary transplants, at a time when the primary ones had ceased to function, and had an average functional period of 1.3 days (1 to 3 days) in 11 dogs. In another series of 10 secondary transplants, Dempster[5] removed the primary transplants on the first to fourth day, usually the fourth, while they were still secreting. The secondary transplants were placed 8 to 28 days after the primary ones. Seven of them functioned for 4 to 5 days. Egdahl and Hume[8] found an average functional period of 1.8 days (0 to 5 days) in 15 secondary renal transplants in mongrel dogs. The primary grafts in this same group had shown an average functional period of 6.2 days, and the secondary transplants had been performed 14 to 133 days after the first.

In none of the 26 instances in which functional periods were measured for both primary and secondary transplants did the secondary graft function for a longer period than the primary,[7] though there was a tendency for the secondary graft to function somewhat longer in animals in which the primary grafts had functioned longest. In the present report, a secondary renal transplant is described which functioned for a much longer time than any secondary transplant previously reported, and for a longer time than the primary or any other canine renal primary homotransplant reported.

The 2 dogs were obtained from our usual sources for mongrel dogs, but showed recognizable characteristics of relatively pure boxer ancestry. The dogs bore no more than a superficial resemblance to each other, however. The right kidney of Dog 1 was removed and a transplant from Dog 2 was placed in the renal fossa with the ureter brought to the skin by methods previously described.[10] A prolonged survival of the primary transplant was noted, with a 24-hour output of 500 ml. of clear urine on the twenty-first day and a continuous secretion for 39 days. Collections after the twenty-first day were incomplete because the suture holding the catheter in place cut through the ureter at this time, and the tip of the ureter retracted back to the skin. On the fifty-first day after transplanta-

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tion, the primary transplant was removed. Both artery and vein were patent. A secondary transplant from Dog 2 was placed in the pelvic fossa, and the remaining kidney of Dog 1 was transferred in the same manner to Dog 2. The ureter of each kidney was anastomosed to the bladder. Both animals were thus bilaterally nephrectomized. Dog 1 was maintained solely by a secondary transplant from Dog 2, and Dog 2 solely by a primary transplant from Dog 1.

Both animals continued to eat ravenously, had intestinal worms and diarrhea, lost weight, and had dependent edema and generalized eczema which tended to clear as the blood urea nitrogen (BUN) approached a more normal level.

Dog 2 (primary transplant from Dog 1) survived 60 days and died from an acute gastrointestinal hemorrhage from an undiscovered site. At the time of death, there was 80 ml. of urine in the bladder.

Dog 1 survived 88 days, during all of which time the secondary transplant continued to function. The cause of death was volvulus of the small intestine which was due to an adhesive band. The blood pressure was 100/60 on day 57. The general condition of the animal appeared better than that of Dog 2 and the eczema cleared more as the BUN level came down. The BUN levels during the course of the experiment are shown in Fig. 1. It is apparent that there was a progressive decline in the BUN level in both dogs after the peak levels were noted by the third week. Both dogs showed an elevation of the BUN to over 180 mg. per 100 ml. by the third week, which declined to 70 mg. per 100 ml. by the fifty-eighth day in Dog 2 and to 40 mg. per 100 ml. on the eighty-sixth day in Dog 1. Table I shows the blood and urine chemistry determinations for Dog 1 on day 56 after the secondary transplantation.

The microscopic appearance of the renal homograft is shown in Figs. 2 through 5. The primary transplant in Dog 1 showed a moderate homograft reaction on day 27 (Fig. 2) and by day 45 (Fig. 3) the kidney was nearly destroyed. The secondary transplant in Dog 1 showed a homograft rejection pattern when biopsied on day 8 (Fig. 4) and this was still present at death on the eighty-eighth day, but there was considerably less round-cell infiltration at this time than had been seen at the earlier biopsy (Fig. 5).

The primary transplant in Dog 2 showed a typical homograft reaction on day 13, which appeared more intense than that seen at

Table I. *Urine and blood values, Dog 1, day 56*

	Urine	*Blood*
Sodium (mEq.)	26	144
Potassium (mEq.)	86	5.3
Chloride (mg.%)	45	106
Creatinine (mg.%)	53	1.3
Urea nitrogen (mg.%)	1,100	—
BUN (mg.%)	—	57

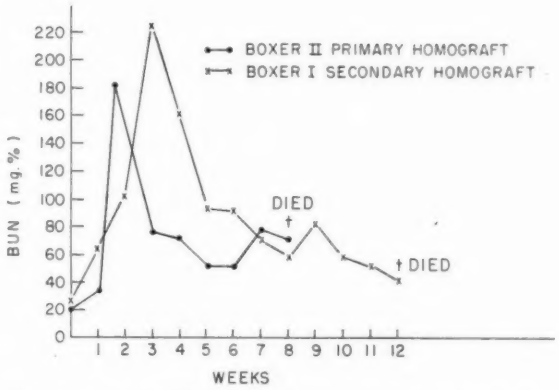

Fig. 1. The BUN levels during the course of the experiment.

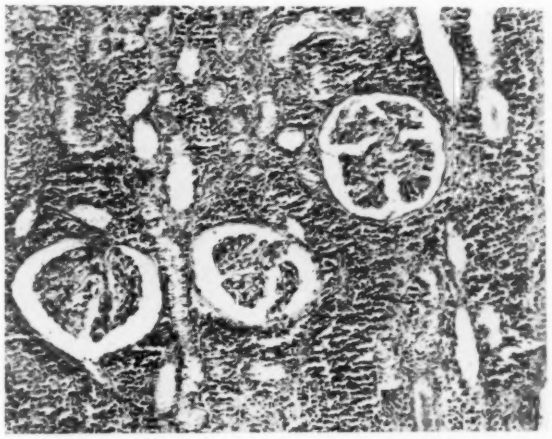

Fig. 2. Dog 1. Biopsy specimen of primary kidney transplant on twenty-seventh day. (Hematoxylin and eosin; × 100; reduced ¾.)

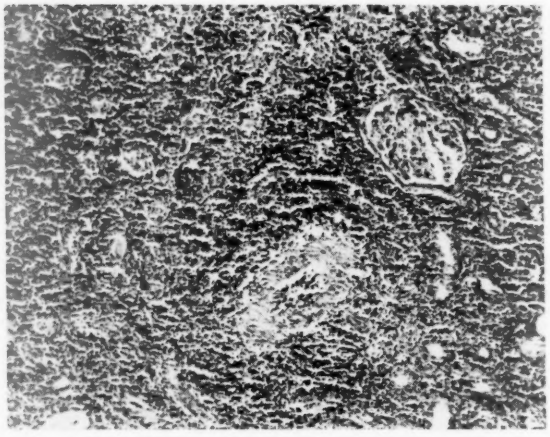

Fig. 3. Dog 1. Biopsy specimen of primary kidney transplant on the forty-fifth day. (Hematoxylin and eosin; × 100; reduced 3/7.)

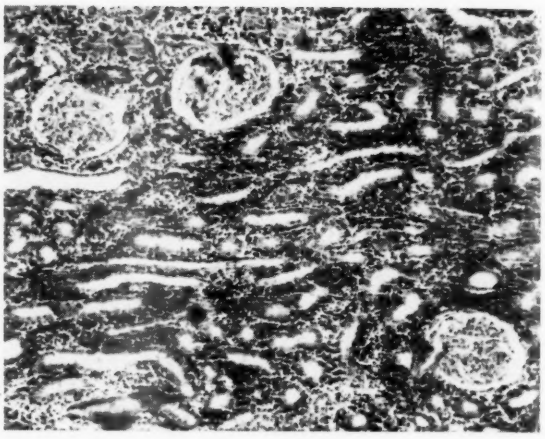

Fig. 4. Biopsy specimen on eighth day of secondary renal transplant in Dog 1. (Hematoxylin and eosin; × 100; reduced 3/7.)

Fig. 5. The secondary renal homograft at eighty-eighth day. (Hematoxylin and eosin, × 100; reduced 3/7.)

Fig. 6. Dog 2. The primary renal homograft on the sixtieth day. (Hematoxylin and eosin; × 100; reduced 3/7.)

death on day 60. At death (Fig. 6) there was infarcation and hyalinization of some glomeruli, while others appeared hypertrophied. There was relatively little round-cell infiltration, and tubular damage, while present, was not complete.

DISCUSSION

The production of acquired immunologic tolerance to homografts has been demonstrated in several species of animals by exposing them to antigens during immunologic immaturity. Tolerance has also apparently been achieved under some circumstances in the adult animal by prolonged antigenic exposure, or prior antigenic exposure with a prolonged interval before grafting. Werder and Hardin[18] showed that in the mouse, repeated homografts of skin from different donors to the same host permit prolonged survival of the later transplants provided that the interval between transplants was long enough. Billingham and Sparrow[2] showed that prolonged "take" of rabbit skin homografts followed pretreatment of the host with epidermal cells from the prospective donor. A secondary transplant from the same donor also showed prolonged survival, sometimes longer than that of the primary. Billingham and associates[1] performed second-

ary grafts in 16 mice in which the primary graft "take" had been prolonged and noted that the secondary grafts survived longer than would ordinarily be expected, but not as long as the primary grafts in the same animal. Martinez and colleagues[14] have demonstrated tolerance to a skin graft transferred between mice in parabiosis. The skin graft placed during the parabiotic union persisted after the termination of this union, and future grafts from the same donor were not rejected. A secondary homotransplant between dogs placed in cross-circulation has persisted without evidences of rejection for 4 days.[9] It appears, therefore, that the dose of the antigen and the time of the exposure to the primary graft may influence the survival of the secondary transplant. In the experiment reported here, the primary renal homograft in Dog 1 remained in place for 51 days and during this entire time both artery and vein were patent in spite of the fact that the kidney had been completely destroyed by a typical homograft reaction. It is possible that this prolonged intravenous exposure to the antigens of the transplant may have induced a state of partial tolerance somewhat like that seen by Martinez[14] in parabiotic mice.

It is also of interest that the primary transplant from Dog 1 into Dog 2 appeared to have had a prolonged survival, although its function was not as good as that of the secondary transplant and its ultimate destruction seems to have been more complete. It is possible that the prolonged survival of this graft may have simply reflected the state of partial compatibility that must have existed between the 2 animals, though it is possible that its exposure during the time that it resided in Dog 1 to the antigens from the renal homotransplant from Dog 2 may in some way have conditioned its response to the subsequent transplantation into Dog 2.

In other experiments in our laboratory, it was found that bilaterally nephrectomized dogs survived an average of 7.5 days.[19] This corresponds well to the figure of 7.8 days found by Dempster.[6] Ten bilaterally nephrectomized dogs with a pelvic renal homotransplant survived an average time of 15 days, with a range from 9 to 25 days.[19] Not only did the 88-day survival period for the secondary transplant reported greatly exceed these survival times, but it was noteworthy that there was a continued rise of the BUN level during the lifespan of the bilaterally nephrectomized animals with transplants, while in the experiment reported here the BUN level fell progressively after the third week. Although the prolonged survival of human renal[11] or skin[3] homotransplants, or dog[12] renal homotransplants may be related to a state of chronic uremia, this mechanism was not operative in the present experiments because the animals were not uremic at the time of transplantation and the progressive uremia in the dogs which had pelvic renal homotransplants without prolonged survival was much greater than in this pair.

In general, the closer the genetic relationship between 2 animals, the longer the survival of the graft.[17] Skin grafts between human fraternal twins will survive 3 times as long as those between unrelated human donors, and a renal transplant between 1 pair of dizygotic human twins appears to have been permanently accepted.[4] This is not always true in the human being, however, because in at least 1 instance a renal transplant between a mother and her son was very rapidly rejected[16] while a markedly prolonged survival was achieved for a renal transplant from a completely unrelated person.[11] Furthermore, in animals no prolongation of survival of renal homotransplants was noted when purebred greyhounds[6] or purebred beagles[13] were used. We cannot absolutely rule out the possibility that the 2 animals used by us were related, although this is extremely unlikely. We have failed to achieve prolonged primary renal homograft function in transplants between 2 other pairs of boxer dogs. Other workers have performed renal homotransplants between litter-mate dogs and have shown that prolonged functional survival does not occur.[12] Therefore, it is unlikely that genetic similarity due to closeness of breeding was a factor in the results described here.

SUMMARY AND CONCLUSIONS

1. Rejection of a secondary renal homotransplant is not always more rapid or more severe than the rejection of the corresponding primary graft.

2. A secondary canine renal homotransplant is reported which maintained a bilateral nephrectomized dog for 88 days, at which time the animal died from causes unrelated to renal failure. There was functional and anatomic evidence of continued survival of the homograft at this time. Microscopically, the homograft reaction was less prominent on the eighty-eighth day than it had been in the biopsy specimen taken on the eighth day after secondary homotransplantation.

3. Although the primary transplant between these 2 animals showed a prolonged survival, it had been completely destroyed by the fifty-first day. The crossed primary transplant from the recipient of the secondary transplant back into the donor also showed a prolonged survival, but not as long and with less adequate function than that seen for the secondary transplant.

4. It is suggested that a state of partial immunologic tolerance of the recipient may have occurred in this experiment as a consequence, perhaps, of prolonged survival of the primary homotransplant.

REFERENCES

1. Billingham, R. E., Brent, L., and Medawar, P. B.: Quantitative studies on tissue transplantation immunity, Phil. Tr. Bull. **239:** 357, 1956.
2. Billingham, R. E., and Sparrow, E.: The effect of prior intravenous injections of dissociated epidermal cells and blood on the survival of skin homografts in rabbits, J. Embryol. & Exper. Morphol. **3:** 265, 1955.
3. Dammin, G. J., Couch, N. P., and Murray, J. E.: Prolonged survival of skin homografts in uremic patients, Ann. New York Acad. Sc. **64:** 967, 1957.
4. Dealy, J. B., Jr., Dammin, G. J., Murray, J. E., and Merrill, J. P.: Total body irradiation in man: tissue patterns observed in attempts to increase the receptivity of renal homografts, Ann. New York Acad. Sc. **87:** 572, 1960.
5. Dempster, W. J.: A consideration of the cause of functional arrest of homotransplanted kidneys, Brit. J. Urol. **27:** 66, 1955.
6. Dempster, W. J.: Kidney homotransplantation, Brit. J. Surg. **40:** 447, 1953.
7. Egdahl, R. H., and Hume, D. M.: Immunological studies in renal homotransplantation, Surg. Gynec. & Obst. **102:** 450, 1956.
8. Egdahl, R. H., and Hume, D. M.: Secondary kidney homotransplantation, S. Forum 6: 423, 1955.
9. Egdahl, R. H., and Hume, D. M.: Studies on kidney homotransplant rejection using a cross-circulation technique, Ann. New York Acad. Sc. **64:** 950, 1957.
10. Hume, D. M., and Egdahl, R. H.: Progressive destruction of renal homografts isolated from the regional lymphatics of the host, SURGERY **38:** 194, 1955.
11. Hume, D. M., Merrill, J. P., Miller, B. F., and Thron, G. W.: Experiences with renal homotransplantation in the human: report of nine cases, J. Clin. Invest. **34:** 327, 1955.
12. Mannick, J. A.: Personal communication.
13. Mannick, J. A., Lochte, H. L., Ashley, C. A., Thomas, E. D., and Ferrebee, J.: A functioning kidney homotransplant in the dog, SURGERY **46:** 821, 1959.
14. Martinez, C., Shapiro, F., and Good, R. A.: Essential duration of parabiosis and development of tolerance to skin homografts in mice, Proc. Soc. Exper. Biol. & Med. **104:** 256, 1960.
15. Medawar, P. B.: The behavior and fate of skin autografts and skin homografts in rabbits, J. Anat. **78:** 176, 1944.
16. Oeconomos, N., Hamburger, J., Delinotte, P., Voysse, J., and others: Attempted homograft (maternal kidney) after nephrectomy because of trauma to a solitary kidney, Internat. Abst. Surg. **98:** 570, 1954.
17. Rogers, B. O.: The genetics of skin homotransplantation in the human, Ann. New York Acad. Sc. **64:** 741, 1957.
18. Werder, A. A., and Hardin, C. A.: A study of consecutively homografted skin on CFW mice, SURGERY **36:** 371, 1954.
19. Zukoski, C. F., Lee, H. M., and Hume, D. M.: The effect of 6-mercaptopurine on renal homograft survival in the dog, Surg. Gynec. & Obst. **112:** 707, 1961.

Theme and variations on blood oxygenators
I. Bubble oxygenators

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There are no new ideas in medicine, just new applications of old themes—at least this study seems to suggest that this is true. Extracorporeal circulation is now a routine procedure in the operating room, but it took 150 years to make it so. What were the important steps in this transition? The idea had to be conceived and the methods for accomplishment of this objective had to be developed. This initially was the role of physiologists who were interested in the study of isolated organs. Probably the most important single factor which made extracorporeal circulation feasible clinically was the discovery and isolation of the natural anticoagulant, heparin. A receptive and talented surgeon with foresight was then necessary who could envision an intact, surviving patient beyond the isolated organ studies. The development of modern blood banking methods was the final step in the evolution of successful extracorporeal circulation.

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*Established Investigator, American Heart Association.

Good historical references on oxygenators

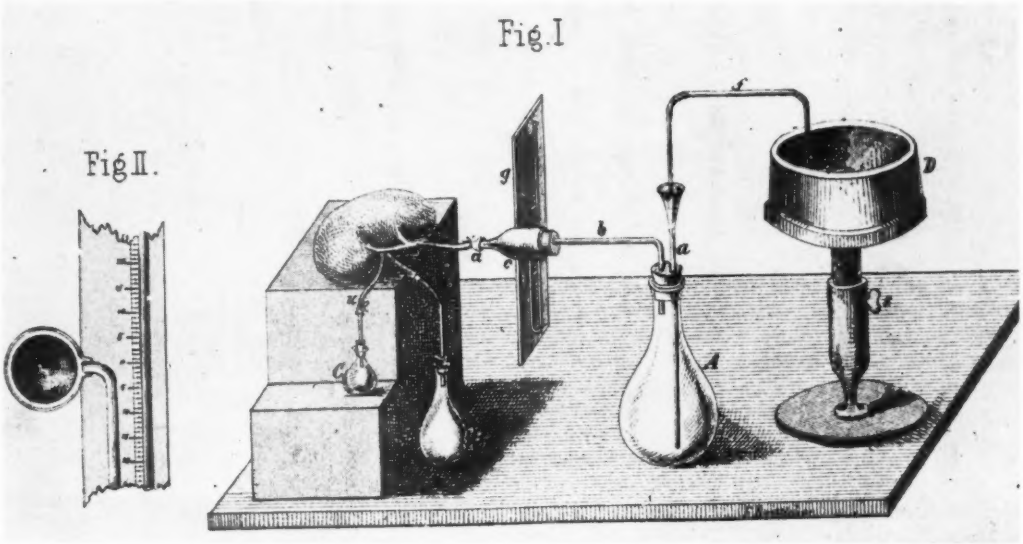

Fig. 1. Bidder used defibrinated blood removed from an artery of a donor animal and placed in a closed vessel marked *A*. Mercury was then introduced from vessel *D* to *A* by means of a siphon, draining the blood through tube *B-C* and *A* to perfuse the isolated organ. A manometer marked *G* measured perfusion pressures. (From E. Bidder.[1])

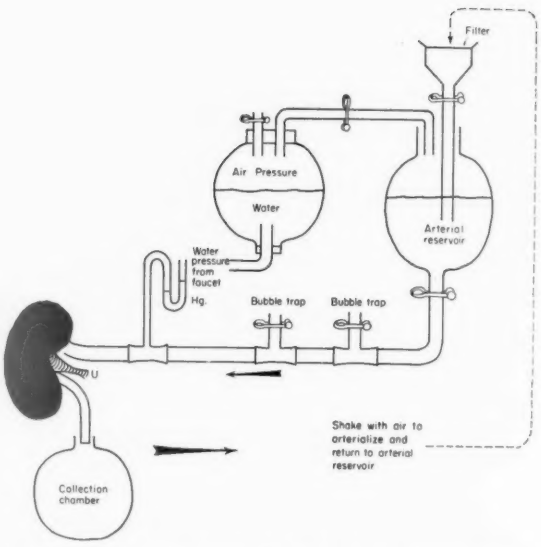

Fig. 2. The apparatus of Bunge. Oxygenation of the blood was accomplished by shaking the venous blood in a large vessel and returning it to an arterial reservoir from which it was forced to the isolated organ.

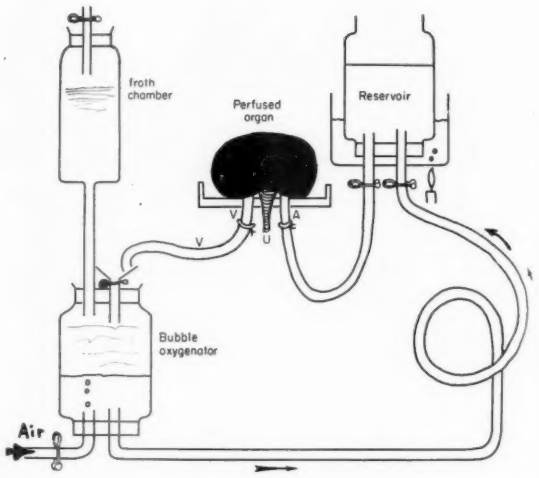

Fig. 3. In Schröder's system, gas was bubbled into venous blood and the oxygenated blood was then driven to a reservoir from which it was perfused to an isolated organ by means of hydrostatic pressure.

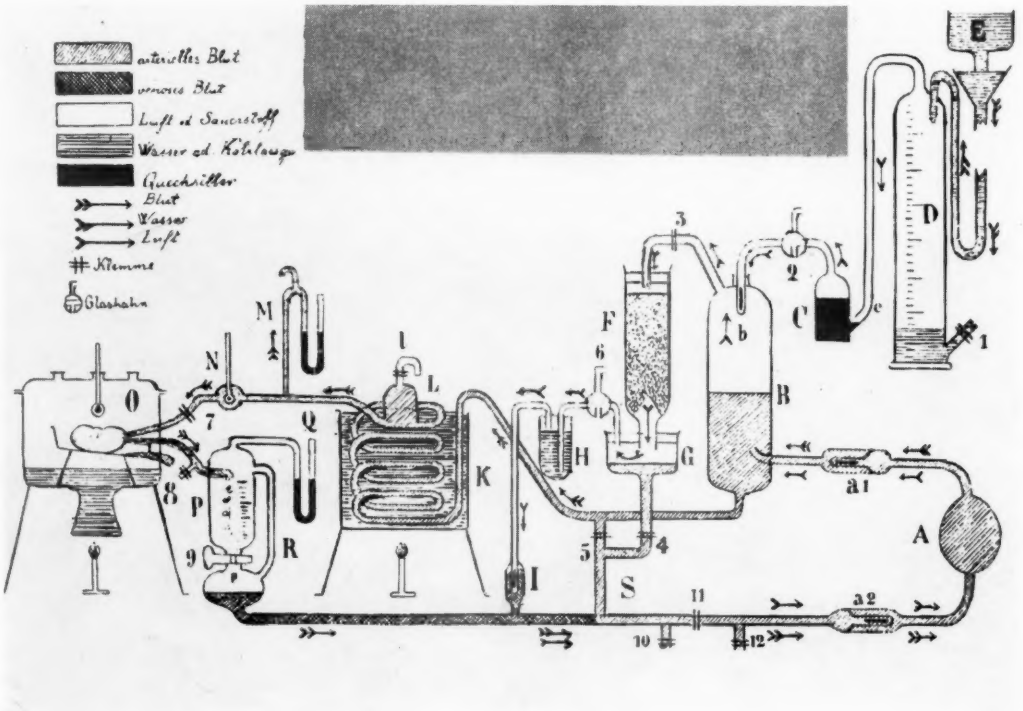

Fig. 4. Jacobi's apparatus. Beginning at upper right, *E,* water pressure system to drive the oxygenating gas by displacing it from vessel *D; D,* graduate to measure the quantity of gas; *C,* mercury valve; *B,* air and blood reservoir; *F,* sand-filled chamber to coalesce foam which passes from *b; H,* alkali chamber to absorb carbon dioxide; *I,* oxygen introduced into the venous blood; *A,* bladder pump for the oxygenated blood; *K,* water bath and coil to maintain blood temperature; *O,* chamber for isolated organ, and *P,* flowmeter. (From C. Jacobj.[15])

were gathered by Skatul,[25] Skramlik,[24] Björk,[2] and Karlson.[16] However there is no available collection of the original diagrams which illustrate the transition of the ideas concerning the extracorporeal oxygenation of blood. We have included these original diagrams when possible.

Our study is concerned with bubble and film oxygenators, excluding the biologic (homologous lung and so forth), chemical, and membrane systems. No attempt is to be made to show all of the variations, especially those of more recent years, but only to indicate the different patterns which have been conceived.

FACTORS CONSIDERED IN CONSTRUCTION OF AN OXYGENATOR

All oxygenators subscribed more or less to a single theme—a respiratory gas mixture must be placed in close relationship to blood. The reaction time between hemoglobin and oxygen is less than one-tenth of a second and for practical purposes less than one-hundredth of a second.[11, 12] Consequently this is not a limiting factor in the construction of an efficient oxygenator. The gas diffusion coefficient is the quantity of that gas that will diffuse across the plane of unit dimensions in unit time under unit concentration gradient. Oxygen must pass through the plasma and the red blood cell membrane in order to react with hemoglobin (excluding the pulmonary membrane; this is not a problem with these oxygenators). An oxygenator must therefore create a film of blood of maximal area and minimal thickness and expose it to an oxygen-containing gas phase under pressure of from 0.2 to 3 atmospheres.

Carbon dioxide is eliminated from the systems by one of two means. One method which is not currently used in oxygenators is passage of the gas through a carbon dioxide–absorbing solution, usually an alkali. The currently preferred method is to allow its escape from the blood by simple diffusion into an atmosphere which contains a concentration of carbon dioxide lower than that of the blood.

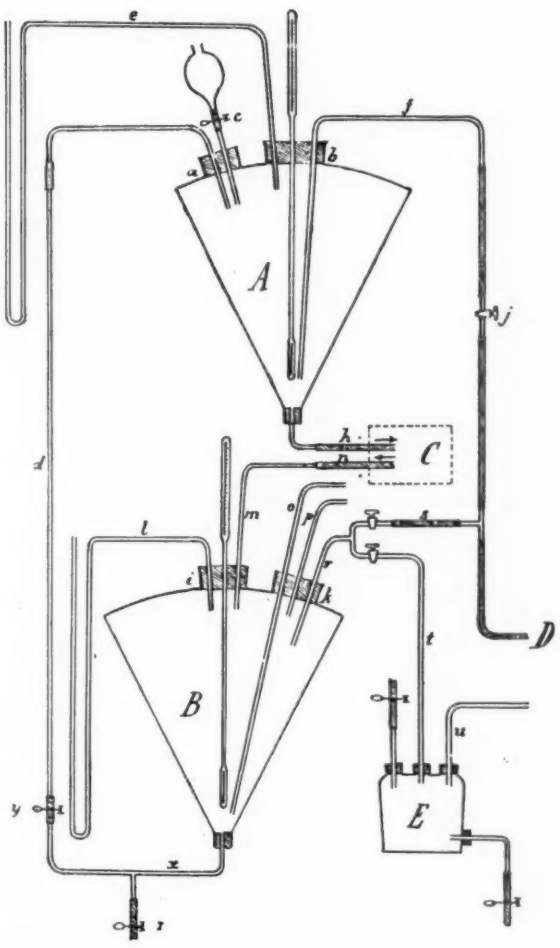

Fig. 5. Salaskin's oxygenator. *A*, Arterial reservoir; *C*, chamber for isolated organ; *D*, gas inlet to create a perfusion pressure; *E*, overflow chamber; *B*, venous reservoir; and *o*, gas inlet to oxygenate blood. (From S. Salaskin.[21])

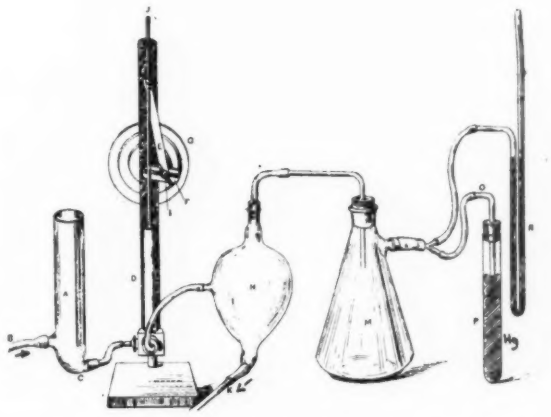

Fig. 6. Brodie's system. *A*, Venous reservoir; *B*, venous inlet; *D*, pump aspirating venous blood and air from *A* and propelling it to *H*, the arterial reservoir; *K*, arterial cannula; and *M*, overflow system for froth. (From T. G. Brodie.[3])

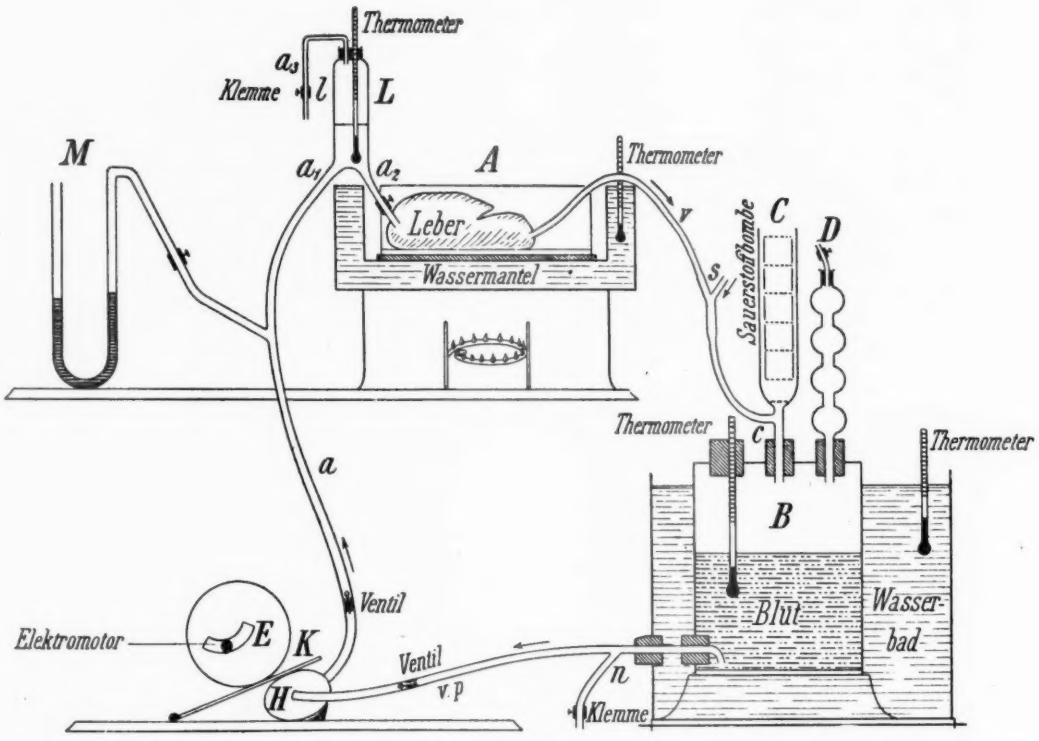

Fig. 7. The Neubauer system. *A*, Chamber for isolated organs; *v*, venous blood; *s*, oxygen inlet; *C*, bubbling chamber containing perforated, paraffin-coated porcelain plates; *D*, froth overflow chamber; and *B*, arterial reservoir. (From O. Neubauer and W. Gross.[20])

Two methods for creating a blood film predominate, the planar or bidimensional methods (film types) and the spherical or 3-dimensional methods (bubble formations). These two methods will be discussed separately.

HISTORICAL REVIEW

The first suggestion of extracorporeal circulation may well be attributed to La-Gallois[17] in 1812. However, the work of Loebell[18] in 1849 seems to be the starting point of more active investigations relating to perfusions. Loebell, whose paper was written in Latin, employed isolated kidney perfusion with defibrinated blood to study the formation of urine and the concentration of solids in renal blood and in urine. He also was one of the first investigators to attempt renal homotransplantation; however, because of his inability to control the clotting of blood in the renal vessels, the transplants failed. He included no diagram of his perfusion system. It may well have been much like that described by Bidder[1] in 1862.

The apparatus of Bidder (Fig. 1) consisted of a reservoir of oxygenated, defibri-

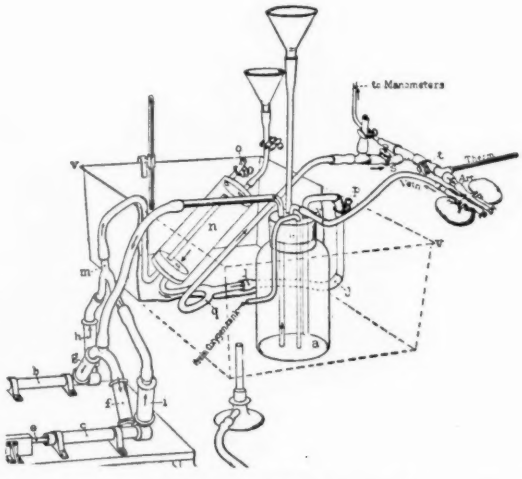

Fig. 8. The oxygenator of Hooker. *a*, Venous reservoir into which oxygen was introduced; *f*, *g*, *h*, pumping system; and *n*, arterial reservoir and debubbling chamber. (From D. R. Hooker.[13])

nated, and filtered blood connected by tubes to an isolated kidney. To obtain oxygenated blood, Bidder bled a donor animal from the carotid artery. The perfusion pressure was created by means of mercury which was transferred from vessel *D* through a siphon *(F)*, displacing the blood from vessel *A*. At a perfusion pressure of 160 to 200 mm. Hg, he obtained a flow rate of approximately 500 ml. one-half hour later. Bidder's work was inspired by that of Loebell in spite of the fact that he did not speak kindly of Loebell's Latin grammar. The low perfusion rates that were observed disturbed him, as did the high pressures necessary for the perfusion.

In 1868, Ludwig and Schmidt,[19] studying metabolism of isolated muscles, also used a mercury displacement method for perfusions as described by Bidder, but added extracorporeal oxygenation of defibrinated blood. This was accomplished by shaking the blood in air.

Bunge and Schmiedeberg[4] published their studies on renal perfusions in 1876, but did not include a diagram of their apparatus. Fig. 2 was created from their word picture. Oxygenation was accomplished by shaking the defibrinated filtered blood in a large glass chamber. The arterialized blood was then deposited in a reservoir from which it flowed to the isolated organ by means of water pressure. Flow rates up to 100 ml. per minute were obtained.

The direct introduction of air into a venous reservoir was described in 1882 by Schröder,[22] and thus the first bubbler came into existence (Fig. 3). By manipulation of the proper clamps, air pressure could be built up in the venous reservoir forcing the bubbled blood into an arterial reservoir from which the isolated organ was perfused.

A rather sophisticated bubble oxygenator was described by Jacobj[15] in 1890 which had a great many attractive features, even by

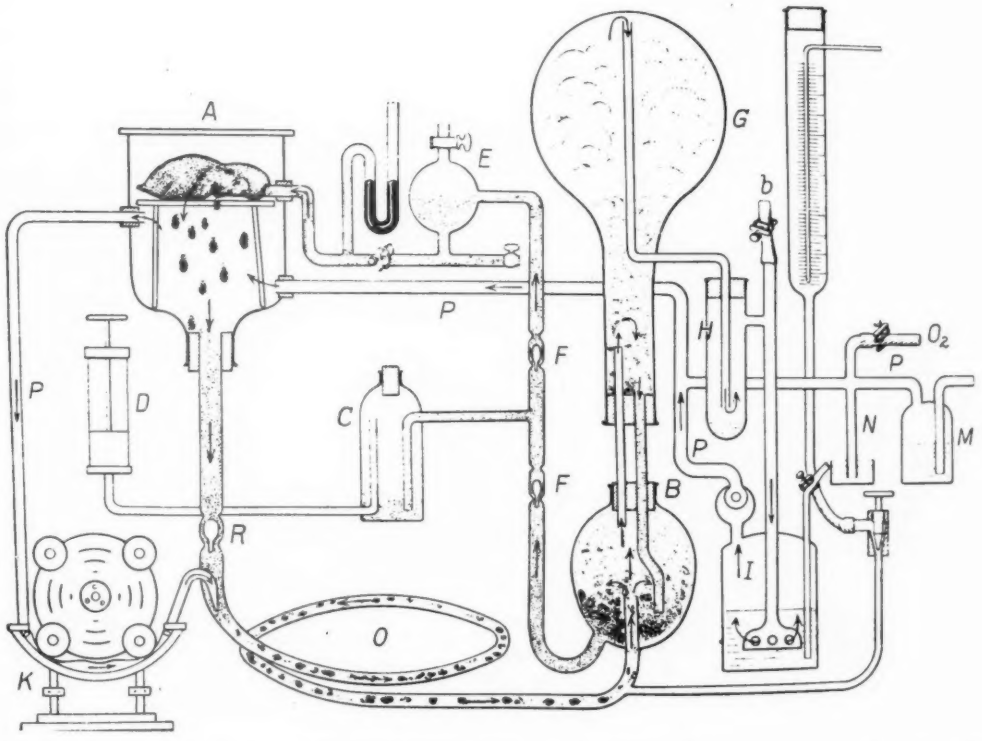

Fig. 9. The Issekutz system. *A*, Chamber for isolated organs; *R*, venous reservoir; *K*, roller pump adding gas to the venous line; *B*, coalescence chamber; *G*, froth chamber; *I*, carbon dioxide–absorbing chamber containing sodium hydroxide; and *E*, bubble separator. The blood flow is maintained by the pressure of the oxygenating gases introduced at point marked O_2. (From B. v. Issekutz.[14])

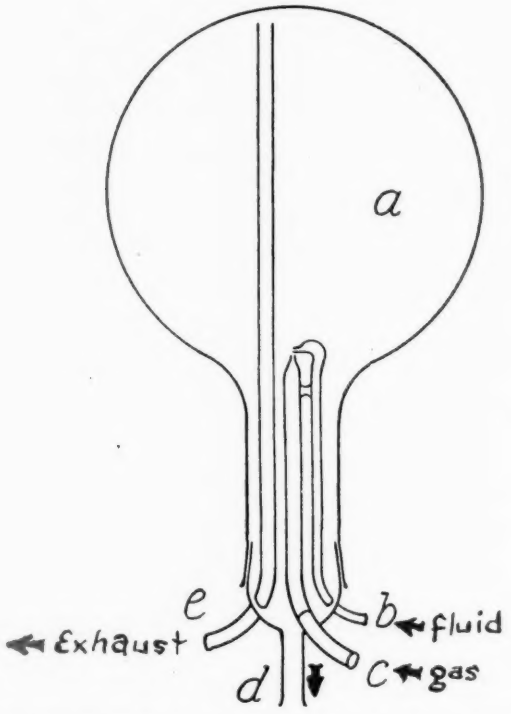

Fig. 10. *A,* Collection chamber for the "atomized" blood; *B,* venous blood inlet and arterialized blood outlet; *C,* gas inlet; *D,* arterial outlet; and *E,* gas exhaust. (From U. S. von Euler and C. Heymans.[27])

present-day standards (Fig. 4). A helical reservoir was used in this system at point *L* both as a debubbling chamber and a heating chamber. Oxygen was directly introduced into venous blood at point *I.* This bubbled blood was then passed through the debubbling system by a bladder pump at point *A.* Point *H* marks a vessel containing sodium hydroxide for the absorption of carbon dioxide. *D* is an air-flow meter. The isolated organ is contained in vessel *O,* and the blood flow is measured by cylinder *P.*

An inverted conical bubble oxygenator was used by Salaskin[21] in 1898 (Fig. 5), but he attributed the design to an associate with whom he had previously worked (Dr. S. Dzierzgowski, *Archives des sciences biologigues de St. Petersburg,* 1897, vol. 41). It was used for metabolism studies of isolated livers contained in vessel *C.* Venous blood was drained into chamber *B* and air or oxygen could be introduced through tube *O.* By means of a hand pump at *D,* air was injected into *B* to raise the pressure sufficiently to move the blood from *B* to *A* and to the isolated organ.

Brodie[3] developed his own modifications of a bubble oxygenator which he described in 1903. This apparatus mixed air with the venous blood by means of a pump as shown in Fig. 6. The pump also served to drive the blood into the isolated organ. The temperature of the blood was maintained at a constant level by placing the apparatus in a water bath. Filtered defibrinated blood was used to prime this apparatus. Because there was some froth formation, a separate foam chamber was connected to the main arterial reservoir, bottle *H.* Heterologous blood was used which did not prove to be satisfactory. Brodie made note of the difficulty in achieving adequate perfusion rates and believed that it was due to persistence of tonus in the arterioles. However, he apparently did not recognize existence of vasotonins in the blood. As an anticoagulant, he used either the Leech extract, hirudin, or blood collected into a sodium citrate solution. The citrated blood, which he thought gave better performance than defibrinated blood, allowed a good flow for several hours. This apparatus at times did not oxygenate adequately.

A model of a well-written scientific paper was presented by Neubauer and Gross[20] in 1910. It described a simple but complete bubble oxygenator as shown in Fig. 7, which provided a perfusion rate of 75 ml. of blood per minute per 100 Gm. of liver. Blood passed from the pump to a bubble trap (*L*) which contained a thermometer and a small glass tube for the escape of air emboli. From *L* it passed to the isolated organ (liver) in a hermetically sealed container kept at a constant temperature by a water bath. The blood left the liver through tube *V,* at which point a controlled source of oxygen was interposed. Aerated and debubbled blood flowed into *B,* after having passed the first debubbling chamber *C* which consisted of a cylinder with several perforated paraffin-coated porcelain plates. Any excess bubbles were allowed to escape into a second debubbler, bottle *D.*

Hooker[13] also used a system which bubbled oxygen directly into the venous blood, vessel *a*, as it left the isolated organ (Fig. 8). A large-bore inclined tube (*n*) was used for a debubbling vessel. The heavier blood sank to the bottom of the vessel and escaped as indicated by the arrow, while the lighter, bubble-containing blood would rise to the top and be evacuated.

Issekutz[14] investigated liver metabolism by an isolated organ perfusion system described in 1927 (Fig. 9). He stated that his work was greatly influenced by Skramlik.[24] This apparatus incorporated another pump to control the introduction of oxygen into the venous blood, and a vessel (*I*) containing sodium hydroxide for the absorption of carbon dioxide.

An "atomizer oxygenator" was described in 1932 by von Euler[27] (Fig. 10). A jet of oxygen or air was directed at a 90 degree angle into a stream of venous blood which was then blown to the walls of a large glass balloon. Von Euler used defibrinated blood after it had been allowed to stand in an icebox for 24 hours in order to inactivate the vasotonins, a precaution described by Bornstein in 1926 for use with his film oxygenator. The capacity of von Euler's oxygenator was 250 ml. per minute. Drying of the finely dispersed blood was encountered which he avoided by saturating the oxygen with water vapor prior to its use. He observed that with the upper degrees of oxygen saturation, small bubbles were liberated from the arterialized blood. This bubble formation could be avoided by keeping the oxygenator at the same temperature as that of the blood.

The apparatus of Thomas[25, 26] created a blood-gas interphase within a layer of quartz sand. The diagram, Fig. 11, is somewhat

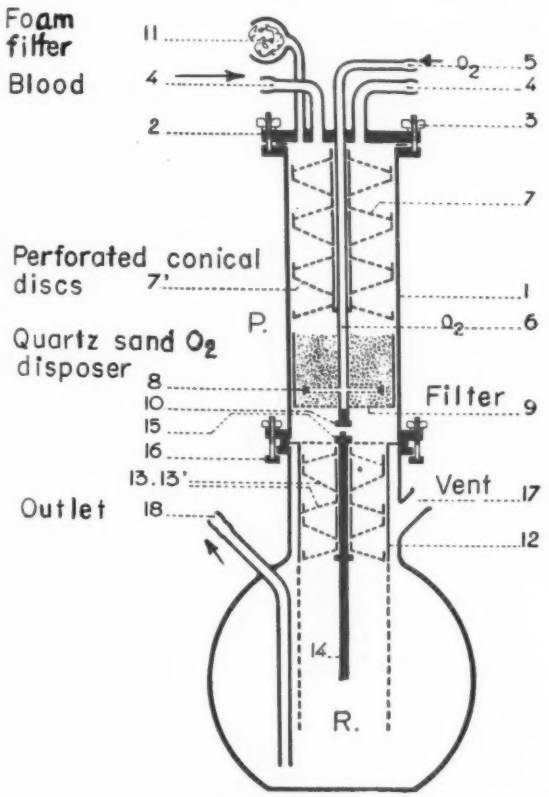

Fig. 11. In the Thomas system, at point *8* venous blood was brought into contact with oxygen through a quartz sand chamber. The arterialized blood then settled through perforated discs to the bottom of the reservoir, *R*. The arterial outlet is at point *18*. (From J. A. Thomas.[26])

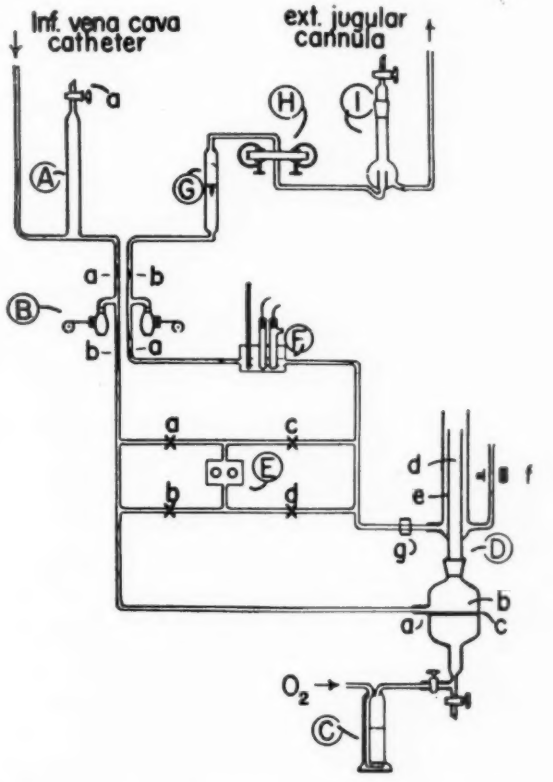

Fig. 12. Clark's apparatus. *A*, Venous blood inlet; *B*, "bottle" pumps; *c*, sintered glass plate to disperse the oxygen into the venous blood; and *d* and *e*, chamber containing silicone for the coalescence of the bubble-containing arterialized blood. (From L. C. Clark, Jr.[5])

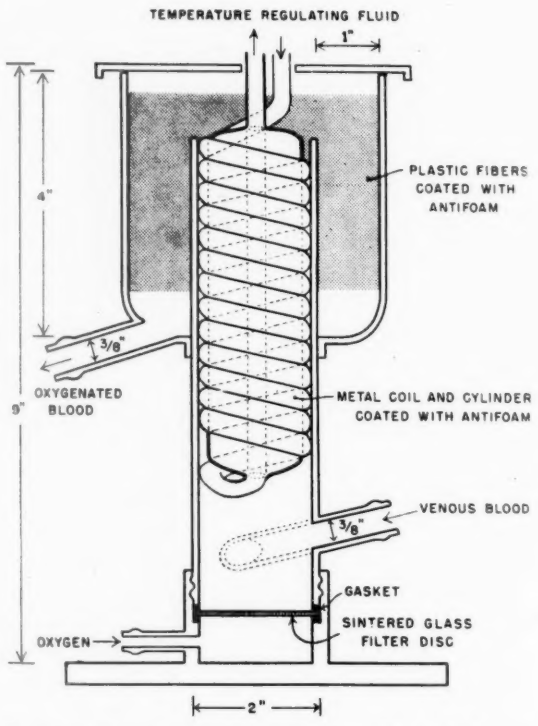

Fig. 13. The perfusion hypothermia bubble oxygenator of Gollan.[11]

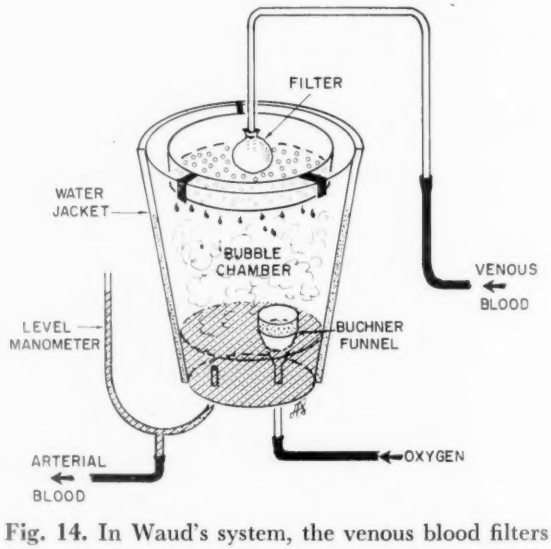

Fig. 14. In Waud's system, the venous blood filters down through the bubble chamber and is collected at the base of the chamber to be evacuated as arterialized blood. (Diagram adapted from original in R. A. Waud.[28])

self-explanatory. Its main application was for isolated organ perfusions.

A paper by Clark and associates[5] in 1950 could certainly be said to have marked the opening of the modern era of the bubble oxygenator. Fig. 12 is a diagram of this system in which oxygen was dispersed through sintered glass filter (*a-c*) to transmit fine bubbles into the venous blood. The major contribution of this paper was the introduction of the silicone defoaming agents. The defoaming agent was used to coat the collection chamber, marked at points *D* and *E* of their system.

The first human application of a pump-oxygenator was in August of 1951, at which time Dogliotte[8] performed a partial bypass on a patient with mediastinal tumor. The blood was removed from the brachial vein and returned to the brachial artery after passing through the oxygenator. The apparatus of Dogliotte was similar to Clark's.

Gollan[10] let his imagination go in 1952 to produce some fascinating experiments which anticipated clinical surgery by at least 5 years. His experiments demonstrated that perfusion hypothermia was practical with the aid of a pump-oxygenator. Fig. 13 illustrates the Gollan oxygenator.

The experiments of Waud[28] and Gimbel,[9] both writing in 1952, produced oxygenators which were similar in principle and which

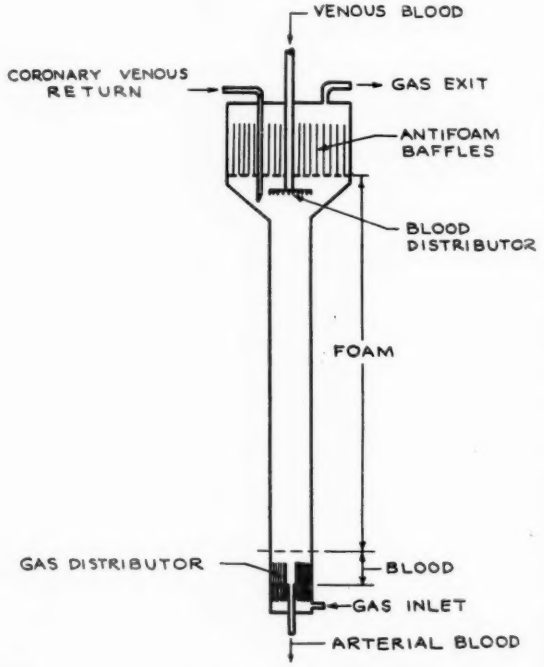

Fig. 15. In Gimbel's oxygenator, venous blood passes through a foam chamber to be evacuated at the base of the oxygenator as arterialized blood. (From S. Gimbel and J. Engelberg.[9])

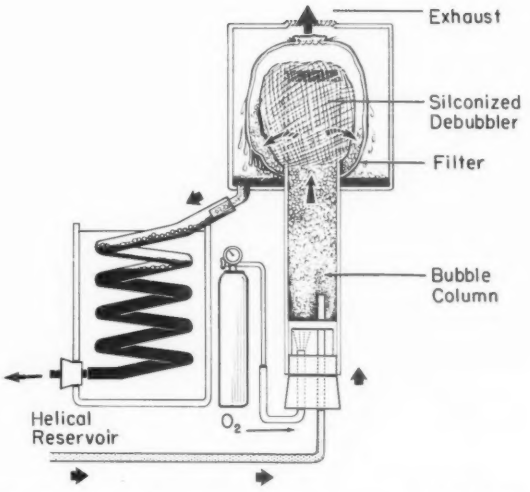

Fig. 16. Perfusion hypothermia system of Zuhdi[29] which employs 5 per cent dextrose to prime the oxygenator in a quantity equivalent to one-third of the patient's daily fluid requirement. No blood is required for operation of the perfusion apparatus as described by Zuhdi.

greatly influenced experimentors that followed. Fig. 14 is a diagram of the Waud apparatus and Fig. 15 is the system described by Gimbel.

The helical reservoir bubble oxygenator[7] (Fig. 16) has been in use at the University of Minnesota since May of 1955 and has been applied to over 1,500 patients for successful perfusions, some of which lasted for over 3 hours. A silicone debubbling chamber is used to disperse the bubbles. A helical reservoir serves to clear the blood of any free gas before it reaches the arterial pump at the base of the helix. Hydrostatic pressure equivalent to the height of blood in the coils causes any free gas to rise upward. Several coils of the helix are maintained full of blood during its operation. The inclined plane of the coil causes the arterialized blood to flow in a laminar fashion down the tube forming a trap for any gas not in solution or in combination with hemoglobin.

Cooley,[6] in 1958, incorporated a helical trough joining the bubbling chamber to the reservoir which served to prevent the free fall of blood from the upper to the lower reservoir (Fig. 17).

Zuhdi[29] described a double helical bubble oxygenator in 1959 (Fig. 18). The inner metal helix carried a thermostatically controlled fluid which allowed simply controlled hypothermia of the blood carried in the outer helix. With this technique he was able

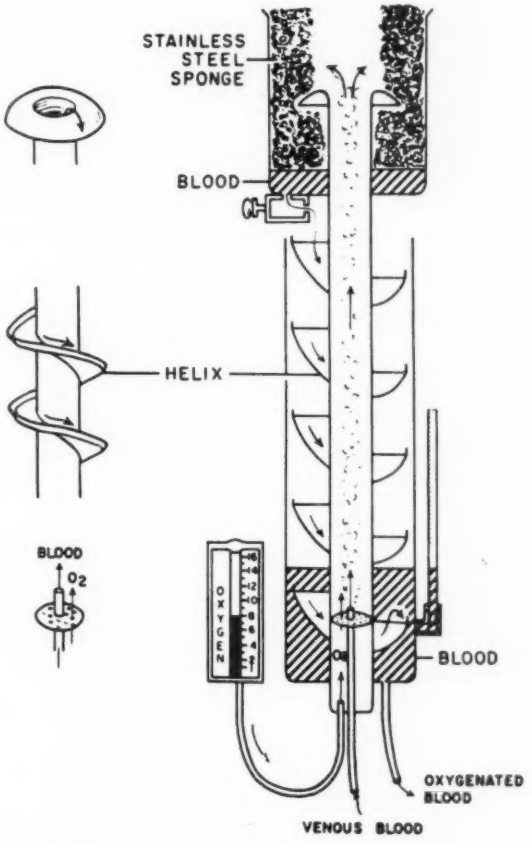

Fig. 17. The helical trough oxygenator of Cooley.[6]

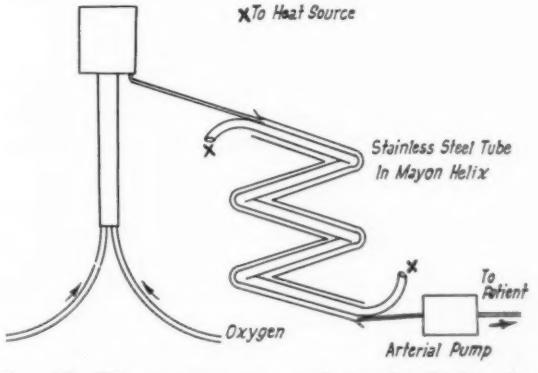

Fig. 18. The oxygenator used at the University of Minnesota. Oxygen and venous blood are introduced at the base of a vertical plastic column. The silicone-coated chamber coalesces the oxygenated blood and releases the excess carbon dioxide through its top. The arterialized blood then passes to a helical reservoir which serves as a final bubble separator, reservoir, and temperature control chamber.

to prime his system with 5 per cent dextrose and utilize only the patient's own blood volume which reduced blood requirements to a minimum.

CONCLUSION

Bubble oxygenators are currently in use at many centers here and abroad. The bubble oxygenator has attained a youthful maturity. However, it is apparent that changes have evolved periodically over the last 100 years. In the future one can only expect a continuing metamorphosis of the designs.

REFERENCES

1. Bidder, E.: Beiträge zur Lehre von der Function der Nieren. Inaugural dissertation, Dorpat, 1862.
2. Björk, V. O.: Brain perfusions with artificially oxygenated blood, Acta chir. scandinav. **96:** 1, 1948.
3. Brodie, T. G.: The perfusion of surviving organs, J. Physiol. 29: 266, 1903.
4. Bunge, G., and Schmiedeberg,, O.: Über die Bildung der Hippursaure, Arch. exper. Path. Pharmakol. **6:** 233, 1876.
5. Clark, L. C., Jr., Gollan, F., and Vishwa, B.: The oxygenation of blood by gas dispersion, Science **111:** 85, 1950.
6. Cooley, D. A., Belmonte, B. A., Latson, J. R., and Pierce, J. F.: Bubble diffusion oxygenator for cardiopulmonary bypass, J. Thoracic Surg. **35:** 131, 1958.
7. DeWall, R. A., Warden, H., Varco, R. L., and Lillehei, C. W.: The Helix reservoir pump oxygenator, Surg. Gynec. & Obst. **104:** 699, 710, 1957.
8. Dogliotti, A. M., and Costantini, A.: Primo caso di applicazione all'uomo un apparecchio di circolazione sanguigna extracorporea, Minerva Chir. **6:** 657, 1951.
9. Gimbel, N. S., and Engelberg, J.: An oxygenator for use in a heart-lung apparatus, S. Forum (1952) pp. 154-157, 1953.
10. Gollan, F., Blos, P., and Schuman, H.: Exclusion of heart and lungs from circulation in the hypothermic closed chest dog by means of a pump-oxygenator, J. Appl. Physiol. **5:** 180, 1952.
11. Hartridge, H., and Roughton, F. J. W.: The kinetics of haemoglobin. II. The velocity with which oxygen dissociates from its combination with haemoglobin, Proc. Roy. Soc. **104:** 395, 1923.
12. Hartridge, H., and Roughton, F. J. W.: The rate of distribution of dissolved gases between the red blood corpuscle and its fluid environment, J. Physiol. **62:** 232, 1927.
13. Hooker, D. R.: A study of the isolated kidney—the influence of pulse pressure upon renal function, Am. J. Physiol. **27:** 24, 1910.
14. Issekutz, v. B.: Beiträge zur Wirkung des Insulins, Biochem. Ztschr. **183:** 283, 1927.
15. Jacobj, C.: Apparat zur Durchblutung isolirter Uberlebender Organe, Arch. exper. Path. Pharmakol. **26:** 388, 1890.
16. Karlson, K. E., Dennis, C., Westover, D., and Sanderson, D.: Pump-oxygenator to supplant the heart and lungs for brief periods, SURGERY **29:** 678, 1951.
17. LaGallois, J. J. C.: Quoted by Griffenhagen, G. B., and Hughes, C. H.: The history of the mechanical heart, Smithsonian Report for 1955. Publication No. 4241, pp. 339-356.
18. Loebell, C. E.: De conditionibus quibus secretiones in glandulis perficiuntur, Diss. Marburg., 1849.
19. Ludwig, C., and Schmidt, A.: Das Verhalten der Gase, Welche mit dem Blut durch dem reizbaren Saugethiermuskel strömen, Leipz. Ges. Wissen. Berisht. **20:** 12, 1868.
20. Neubauer, O., and Gross, W.: Zur Kenntniss des Tyrosinabbaus in der kunstlich durchbluteten Leber, Ztschr. physiol. Chem. **67:** 219, 1910.
21. Salaskin, S.: Über die Bildung von Harnstoff in der leber der Saugethiere aus Amidosauren der Frettreihe, Ztschr. physiol. Chem. **25:** 128, 1898.
22. Schröder, W. v.: Über die Bildungsstatte des Harnstoffs, Arch. exper. Path. Pharmakol. **15:** 364, 1882.
23. Skutul, K.: Über Durchstromungsapparate, Arch. ges. Physiol. **123:** 249, 1908.
24. Skramlik, E.: Ein Apparat zur Durchströmung der Leber, Arch. ges. Physiol. **180:** 1, 1920.
25. Thomas, J. A.: Un appareil pour la perfusion steríle et automatique de gros organes ou de parties d' organismes, Ann. Physiol. Physiocochem. Biol. **15:** 432, 1939.
26. Thomas, J. A.: Nouveaux procédés de perfusion physiologique et aseptique permettant la survie prolongée d'organes ou d'organismes pesant plusieurs kilogrammes, J. Physiol. **40:** 123, 1948.
27. Von Euler, U. S., and Heymans, C.: An oxgenator for perfusion experiments, J. Physiol. **74:** 2p, 1932.
28. Waud, R. A.: A mechanical heart and lung, Canad. J. M. Sc. **30:** 130, 1952.
29. Zuhdi, N., Greer, A., Kimmell, G. M., Redmond, R., Donnell, J., Carey, J., Geigerman, D., and Krieger, C.: Clinical study of hypothermic perfusion, J. Oklahoma M. A. **52:** 671, 1959.

The measurement of the pulmonary venous cross-circulation through the conjugated heart of thoracopagous twins with radioactive O^{15}

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The purpose of this article is to report the development of a new technique for measuring the distribution of oxygenated blood coming from the lungs and to report the measurement of the cross-circulation of pulmonarily oxygenated blood through the conjugated heart of thoracopagous twins. The technique for measuring the distribution of oxygenated blood is one developed at the Washington University cyclotron with radioactive O^{15} administered by inhalation to tag the unsaturated hemoglobin circulating through the pulmonary alveoli. The circulation time between the lung and the periphery and the relative concentration of pulmonarily oxygenated blood in the peripheral tissue can be measured with external scintillation counters.

Previously, I^{131}-labeled human serum albumin[3] and tagged red blood cells[1] have been used to measure the cross-circulation between thoracopagous twins. These techniques have proved useful in the estimation of the rates of hemic mixing between the twins, but the use of O^{15} has 2 peculiar advantages. First is the simplicity of the technique. Second, the measurements obtained can be used to assess the cross-circulation of pulmonary venous drainage.

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THE THORACOPAGUS

At birth on Sept. 8, 1960, the thoracopagus, subsequently designated V1 and V2, weighed 4,600 grams. The combined weight on Nov. 18, 1960 (2 days before death), was 4,400 grams, and the maximum weight ever attained was 4,900 grams on Nov. 5, 1960.

During life, physical examination and various radiographic studies determined that the twins possessed separate nervous systems, genitourinary tracts, esophagi, gall bladders, stomachs, duodenums, rectums, colons, tracheobronchial trees, and skeletal systems. A small congenital omphalocele in V2 became covered with skin without surgical intervention (Fig. 1). The crossing of swallowed barium and carmine red into the colon of the second infant established that an enteroenteric communication existed but the extent of the connection was not known with certainty.

The electrocardiographic tracings obtained on each infant are shown in Fig. 2. The anatomic union of the twins precluded an accurate placement of the V leads. These routine tracings did not establish with absolute certainty that a common conduction system existed in the conjoined heart, but the rates and conduction intervals were the same. Furthermore, if the L_1, L_2, aV_R, and aV_L tracings are rotated 90 degrees from the long axis of the tracing, and if the tracings from one infant are faced toward a mirror and the tracings from the other infant are

Fig. 1. Appearance of the conjoined thoracopagous twins on Sept. 9, 1960. The omphalocele of V2 closed without surgical repair.

placed beside the mirror image, the observation that the complete tracings in these leads are almost perfect mirror images of one another can be appreciated. This is very strong evidence for the presence of a single conduction system within the conjugated heart.

On Oct. 29, 1960, an angiocardiogram was performed by the injection of 11 ml. of Hypaque through a polyethylene catheter threaded from a leg vein of V2 through the vena cava of V2 into an auricle of V2. The serial angiograms established that a large communication existed between the hearts of V1 and V2, that a large patent ductus arteriosus existed in V2, that contrast media appeared in the aortae of both infants simultaneously, and that there were at least 2 ventricles. Other minor variations of the arterial outflow tract were noted. No information on the pulmonary venous drainage was obtained.

Cyanosis had been absent at birth but was evident in V2 with straining or crying by the second week of life. Oxygen saturation in the ear lobes of V1 and V2 on Oct. 3, 1960, was 77.5 and 78 per cent, respectively. By Oct. 22, 1960, the twin V2 became distinctly more cyanotic upon crying. By Nov. 15, 1960, the cyanosis of V2 was deeper and continuous. The breathing of nasal oxygen by V2 did not reduce the cyanosis of V2. The twins received digoxin according to their combined weight (0.045 mg. times 4.8 Kg. equals 0.2160 mg. over 48 hours) on November 15 without diminution of the cyanosis. Physical signs of pulmonary edema never developed during life and none were present at necropsy. On Nov. 18, 1960, V2 had a complete but temporary respiratory arrest. On Nov. 19, 1960, V2 passed a tarry stool and some blood was present also in the stool of V1. On Nov. 20, 1960, both twins died of a sudden, simultaneous respiratory and cardiac arrest.

At necropsy the ante mortem observations were confirmed and in addition several anatomic anomalies were noted. First, the splenic veins drained into a common portal vein, which then arborized into each liver at the porta hepatis. Second, the livers were joined only over an area of less than 6 $cm.^2$ and no major blood vessels traversed the parenchymatous junction. Third, the hepatic venous drainage consisted of a large vessel from each liver that joined to form a common channel into the inferior vena cava of V2 draining into auricle 1 (Fig. 3). Fourth, the common bile ducts of each twin joined in a single ampulla of Vater. Fifth, the twins shared a common small intestine from the ampulla of Vater to the ileum and just distal to the ileal bifurcation, twin V2 possessed a Meckel's diverticulum that contained both aberrant pancreatic tissue and gastric mucosa but no demonstrable ulceration. For several days before death the stools of both infants contained blood and at necropsy both colons were found to contain old blood. However, the mucosal surface of the entire intestine appeared normal and no source of bleeding was evident. Each twin

had 2 adrenal glands and each gland weighed approximately 1.5 grams. Atrophy of the adrenal glands in 1 twin had not occurred. The hearts were conjugated in a most complex and obviously inseparable manner (Fig. 3).

MEASUREMENT OF THE CROSS-CIRCULATION OF BLOOD OXYGENATED BY THE BREATHING OF RADIOACTIVE O^{15}

O^{15} is a radioactive isotope of oxygen which has a half-life of 2.25 minutes and decays by the emission of 1.68 mev positrons. The radioactivity from its decay is measurable by externally situated scintillation counters. The measurable radiation counted is 0.51 mev photons arising from the interaction of the positrons with matter. The isotope is produced, purified, and used at the Washington University cyclotron in the form of circulating tagged air. The radioactivity in the tagged air behaves as molecular oxygen with a purity of over 99.4 per cent. The O^{15} is bound proportionally to hemoglobin, enters into oxidative metabolism, and is incorporated rapidly into water of metabolism.[4]

The total irradiation received by the infants during the cross-circulation studies did not exceed 1.0 rad, an amount considerably less than the estimated 10 rads received during the various radiographic studies.

The cross-circulation studies were conducted by placing one of a pair of shielded, balanced scintillation counters over the greater trochanter of each infant. The counting rates were fed through a count rate meter into a 2-channel recorder. Then, 1 infant (V1) breathed flowing air tagged with O^{15} through a standard infant-size anesthetic face mask for several breaths and a continual recording of circulation times from the lungs to the pelves and the relative accumulation of O^{15} in the pelves was made with the scintillation counters. Then, the administration of O^{15} was discontinued, but the recording of the radioactivity in the pelves was continued until radioactivity in each pelvis was in equilibrium. Within 10 half-lives of the isotope (10 times 2.25 minute half-life of oxygen equals 22.5 minutes) all detectable radioactivity disappeared from the infants. Subsequently, the procedure was repeated identically but with the second twin (V2) breathing the tagged air.

Figs. 4 and 5 and Table I contain the data derived from the O^{15} studies performed on Oct. 27, 1960. The conclusions from these data were (1) the pulmonary venous blood from V1 went entirely to the body of infant V1 and entered the body of V2 only after completion of a circulation through the body of V1, (2) one-half of the pulmonary venous drainage from the lungs of V2 entered the peripheral circulation of V1 at the same rate and concentration that the other half entered the body of V2, (3) the cross circulation between the 2 infants was of such great magnitude that complete mixing occurred in 20.5 seconds, and (4) V1

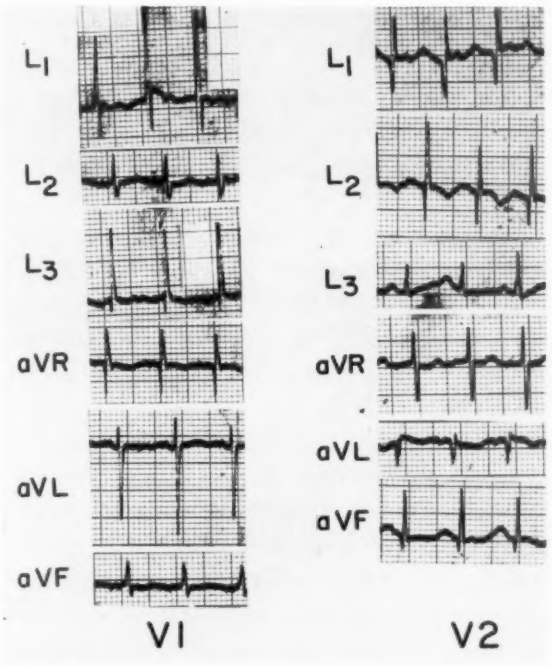

Fig. 2. Admission electrocardiograms. In each twin the P-R interval was 0.11 seconds; the QRS complex, 0.06 seconds, and the ventricular rate, 150 per minute. The direction of all deflections in the alternate leads from each twin are practically mirror images about the longitudinal axes of the tracings. There is some variation in the wave amplitudes of the deflections in the mirror images.

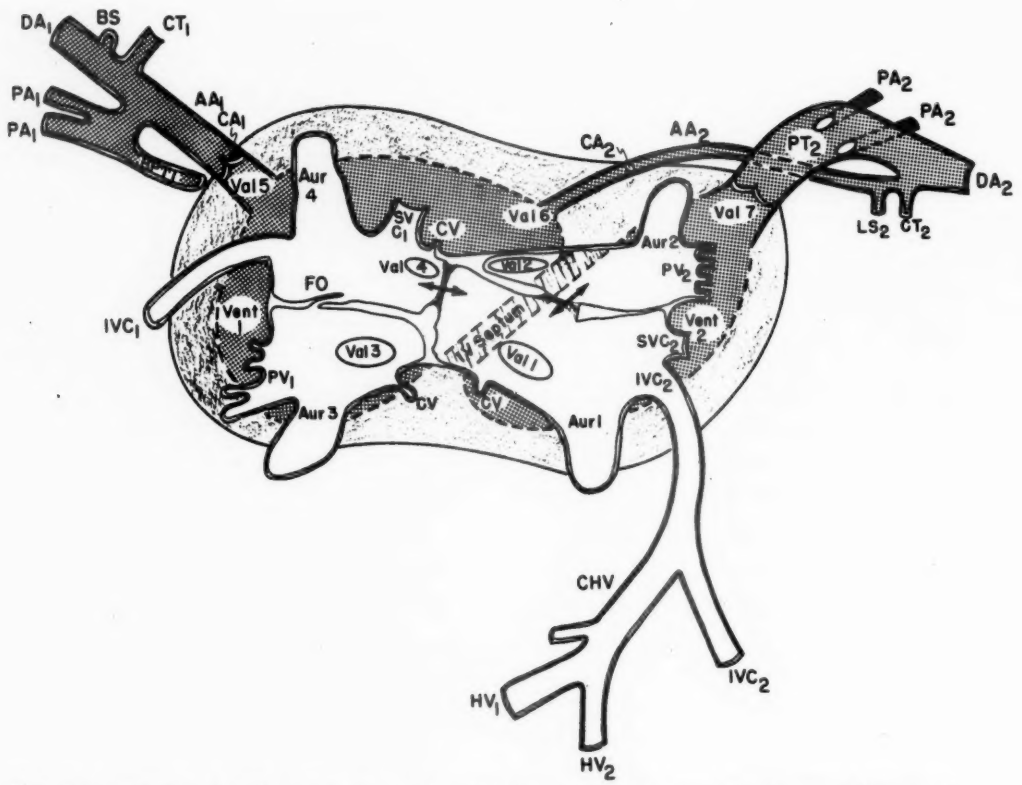

Fig. 3. Anatomic drawing of the conjugated heart viewed from the base of the heart.

was obviously favored over V2 by the cross-circulation of the oxygenated blood.

DISCUSSION

The picture was one of the progressive circulatory dominance of V1 over V2. At birth the infants had been acyanotic and on Oct. 3, 1960, no significant difference existed in the ear-lobe oxygen saturation of either infant. Both had the same degree of anoxia, although by this time V2 became "dusky" with crying. However, by Oct. 27, 1960, V2 became distinctly cyanotic with effort and on this date the O^{15} studies, showing the preferential oxygenation of V1, were performed. Obviously, the hemic mixing was very great in the portal circulations but there must also have been significant mixing of blood among the intercommunicating auricular chambers and in ventricle 1. Had the interauricular septal defects not been present, it is doubtful that V2 would have survived birth. The reason for the latter statement can be seen in the arrangement of the auriculoventricular valves in Fig. 3. Peculiarly, 3 of the 4 auriculoventricular valves, including the auriculoventricular valve from auricle 2 which received the pulmonary venous drainage from infant V2, communicated with ventricle 1. Only 1 auriculoventricular valve *(Val 1)* entered

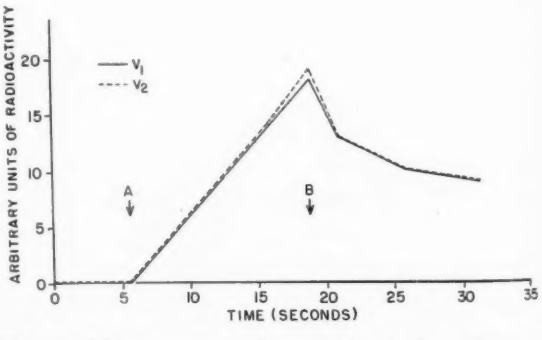

Fig. 4. Measurement of cross-circulation of oxygenated blood from V2. The lines record the relative number of counts per second above background recorded by balanced scintillation counters externally situated over the greater trochanter of each infant. At *0* time V2 began breathing tagged air. At *A* the radioactivity began to accumulate in the pelves. At *B* V2 stopped breathing tagged air.

ventricle 2, and the auricle of origin *(Aur 1)* received only vena caval blood. All of the peripheral arterial blood to twin V1 came from ventricle 1 with partial recirculation into the pulmonary arteries of V1 through the patent ductus arteriosus, and all peripheral arterial blood to twin V2 came from ventricle 2 via the patent ductus from the large pulmonary truncus. The blood going to twin V2 via the atretic aorta (diameter 1 to 2 mm.) from ventricle 1 must have been inconsequential. However, the coronary arterial supply to ventricle 2 did come from this atretic aorta. The ventricular walls and the interventricular septum were hypertrophied and the degree of hypertrophy seemed to compromise further the smaller chamber of ventricle 2.

As a result of the favored status of twin V1 in the cross-circulation, she was receiving all of the pulmonary venous drainage from her own lungs and one-half of the pulmonary venous drainage from twin V2. Twin V2 was receiving only one-half of her own pulmonary venous blood on October 27, and from the progressive deepening of the cyanosis in V2 there is reason to believe that the percentage of pulmonary venous blood received by V2 steadily decreased, ultimately causing a unilateral anoxic respiratory arrest in V2 2 days before the simultaneous infant death from cardiac arrest occurred. That either twin could have been saved even by the surgical sacrifice of the second twin is most unlikely.

Chang Bunker, the alcoholic twin in P. T. Barnum's Siamese twins, inadvertently conducted the first known cross-circulation studies between conjoined twins. In spite of Chang's frequently excessive intake of alcoholic beverages, he never affected the sobriety of his brother Eng, and the physicians of the day concluded that the cross-circulation through the bridge could not be great. The necropsy studies of Chang and Eng seemingly supported this conclusion.[2] The complete mixing of tagged red blood cells between Aird's conjoined twins required 29 minutes,[1] the complete mixing of iodinated serum albumin between the conjoined twins of Peterson and Hill required 10 minutes,[3] and the equilibration of O^{15} in this set of conjoined twins required only 20.5 seconds.

Table I. *The circulation and equilibration times of O^{15} in thoracopagous twins*

Circulation time	*Ratio of maximum radioactivity in pelves*	*Equilibration time*
V1 breathing O^{15}		
Lung of V1 to pelvis of V1, 6.6 sec.; lung of V1 to pelvis of V2, 15.6 sec.	V1:V2 = 2.32:1*	Time required for equilibration of radioactivity in pelves of V1 and V2 after discontinuation of O^{15} inhalation by V1 equals 20.5 sec.
V2 breathing O^{15}		
Lung of V2 to pelvis of V2, 5.7 sec.; lung of V2 to pelvis of V1, 5.7 sec.	V1:V2 = unity at all times	

*Recorded 25.6 seconds after V1 began breathing O^{15}.

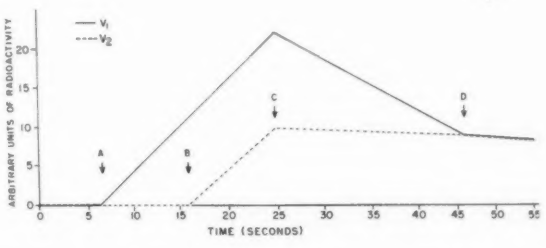

Fig. 5. Measurement of cross-circulation of oxygenated blood from V1. At *0* time V1 began breathing tagged air. At *A* radioactivity began to accumulate in the pelvis of V1 and at *B* in the pelvis of V2. At *C* V1 stopped breathing tagged air. At *D* the activity in the pelves of V1 and V2 became equal.

CONCLUSION

The anatomic detail of the complex cardiac conjugation between conjoined thoracopagous twins is described. Radioactive O^{15} administered by inhalation was used to evaluate the flow and distribution of oxygenated pulmonary venous blood through the conjugated heart and into the periphery of the twins.

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REFERENCES

1. Aird, I.: The conjoined twins of Kano, Brit. M. J. **1:** 831, 1954.
2. Luckhardt, A. B.: Report of the autopsy of the Siamese twins together with interesting information covering their life, Surg. Gynec. & Obst. **72:** 116, 1941.
3. Peterson, C. G., and Hill, A. J.: Separation of conjoined thoracopagus twins, Ann. Surg. **152:** 717, 1960.
4. Ter-Pogossian, M., Spratt, J. S., Jr., Rudman, S., and Spencer, A.: Radioactive oxygen-15 for the study of the kinetics of the oxygen of respiration, Am. J. Physiol. In press.

Arterial prosthesis of collagen-impregnated Dacron tulle

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Arterial surgery has earned a secure, if still poorly defined, niche in the armamentarium of surgical procedures. The scope of arterial replacement within the field of arterial surgery is also poorly defined. In some conditions, the question of arterial replacement does not apply; in others, it is obligatory; in still others, it is elective. For example, in the treatment of most emboli and most traumatic arteriovenous fistulas, the question of arterial replacement does not arise since the patient's own vessel is still employed. When an arterial wall is hopelessly diseased, as in the case of aneurysms, its replacement is mandatory. When an artery is occluded by disease, it may be possible merely to remove the occlusion by endarterectomy or it may be necessary to replace the artery or to bypass the occlusion.

The search for a durable, trustworthy arterial substitute has resulted in extensive programs of laboratory experimentation by many investigators in the past decade. That the ideal prosthesis has not yet been found is testimony to the many technical, biologic, and immunologic difficulties involved. Many materials have been tested. Equine, bovine, and porcine heterografts, autogenous skin, bowel, peritoneum-lined rectus sheath, chamois, silicone, polyvinyl sponge, nylon, Orlon, Dacron, Vinyon-N, and Teflon are among the materials which have been fashioned into conduits and investigated in experimental animals.[1, 4, 5, 14, 16-22, 25-27, 29] Arterial homografts have been extensively studied.[3, 19, 22] Equine heterografts have functioned well in dogs for as long as 2 years,[21] but have disadvantages similar to those of the homograft in man, that is, the formation of aneurysms.[16] The use of skin, bowel, and peritoneum-lined rectus sheath has not proved successful experimentally.[19] Chamois functioned satisfactorily in dogs and was well organized 115 days after implantation.[14] Silicone, because of its elastic properties, seemed attractive but was abandoned because of the prohibitively high incidence of thrombosis.[29] Polyvinyl sponge and Ivalon sponge appeared to be well tolerated by dogs and to organize well, but they lacked the necessary strength for clinical application.[10, 11, 19, 26] Nylon was one of the first materials employed in plastic prostheses. Much experimentation was carried out on types of weave and structure,[7, 10, 11, 19, 23, 25] but nylon has been clinically unsatisfactory because of its great loss of tensile strength after implantation.[12] Orlon at first seemed favorable,[18, 22, 27, 28] but the inelasticity and the high porosity with resultant hemorrhage made this prosthesis unacceptable. Dacron and Teflon have emerged as the most satisfactory plastic prostheses now available. Both have displayed excellent retention of tensile strength over long periods of time and both are essentially in-

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ert,[10, 11] although Teflon is slightly more inert and slightly stronger than Dacron.

GRAFT MATERIAL IN CURRENT CLINICAL USE

Dacron and Teflon. Of the many experimental substitutes, Dacron and Teflon are virtually alone in their clinical use today. In general, the complications associated with each are the same.

Failure of the host tissue to grow to the graft across an anastomotic line leaves the patient dependent to a large degree upon the strength of the suture material used at the anastomosis. Silk, which loses much of its strength in 6 to 12 months, has failed many times, resulting in false aneurysms in the groin and popliteal space and death when disruption occurred in the abdomen. The current availability of Dacron suture material has obviated this problem to a great extent.

Failure of the fibrin lining to organize in the human being makes continuing appositional deposition of blood elements possible with resultant thickening, particularly at an anastomotic line, and final occlusion of the graft. Thickening of the intima frequently occurs at the host side of anastomotic lines, perhaps because of the increased metabolism secondary to an attempt at healing after operation, but the unorganized lining of the present plastic materials adds further to the postoperative stenosis. This is most critical in the smaller femoropopliteal grafts—so much so that femoral grafting, except for emergent need, has been given up by many clinicians in the field. Also, cracking or splitting of the unorganized lining because of such trauma as acute flexion may lead to dissection of the lining and acute occlusion of the lumen.

The fibrous envelope surrounding the graft does not become adherent to the graft and a periprosthetic space persists indefinitely. In more than 40 grafts in the lower extremity, either of Dacron or of Teflon, which for one reason or another we have replaced over periods of time of up to 2½ years, no graft has failed to show this surrounding space. The graft has always been easily removed merely by cutting it at both ends and pulling it through the submuscular or subcutaneous tunnel. The only graft in this group which we found adherent was one which had been thrombosed and therefore nonfunctional for 6 months. Because the periprosthetic space is present, infection at any point may spread rapidly throughout the length of the graft and an infection at a groin insertion of an aortofemoral graft may readily spread and cause rupture at the aortic anastomosis.

All of these problems stem from a common cause—failure of the host tissue to grow to, into, and through the prosthetic replacement. This failure is in contrast to the response of the experimental animal (dog) to these same materials (Fig. 1)[9] and indicates that although the results of canine experimentation are suggestive, there are species differences involved and absolute prediction of human response cannot be made from animal experimentation.

Homograft. The homograft has the advantage of being accepted by the host with ingrowth of host tissue to one-fourth or one-third of its external coat as time goes on. This obviates the first problem of suture-line rupture, since the host tissue grows en-

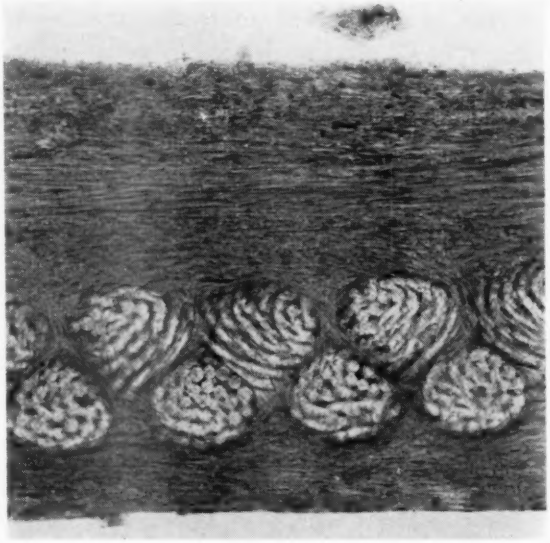

Fig. 1. Longitudinal section of "close-weave" Dacron graft in the dog at 6 months. (From J. Harold Harrison.[9])

tirely around and into the anastomotic line unless the graft is infected before such growth can occur.

However, the inner lining of the graft is nonliving and consists of the internal elastic lamina. There is, then, nothing to prevent appositional thickening, particularly at anastomotic lines, and occlusions occur in small grafts with this material also. Finally, the nonviable state of the homograft wall makes it particularly vulnerable to local infection.

In a small percentage of homografts (less than 2 per cent) aneurysm formation develops either through the use of a graft that has an inherently weak point at the time of implantation, or through weakening resulting from low-grade subclinical infection or tissue degeneration.

Vein grafts are usually autogenous and will not be considered here as a "foreign" substitution material.

THEORETICAL AND PRACTICAL CONSIDERATIONS FOR AN IDEAL PROSTHESIS

It has been an opinion that preservation of the elastica was desirable for continued strength of a homograft or a heterograft. This is open to question. In 1942, Hass[13] extracted aortic rings with formic acid and obtained an intact, purified network of elastic fibers. These showed a high degree of extensibility on stress with almost perfect elastic recoil upon relief of stress. However, these rings were weak and ruptured under loads averaging 80 Gm. Untreated aortic rings did not rupture until many pounds were applied. Krafka,[15] in 1939, showed that the calculation of Young's modulus obtained for the collagen component of the arterial wall was very high when compared with that determined for the musculoelastic portion. The difference was of the order of several hundred times. Burton[2] in 1954, undertook to explain the independent roles of elastica and collagen, and believed that the elastica elongated under minimal load but that arterial expansion was limited by the collagen rather than by the elastica at a predesigned safe point of stretch. Although it is desirable to have an elastic artery to cushion the systolic pressure upon ventricular contraction, this is not a necessity as shown by the many senile sclerotic aortas with nonfunctional elastica and high collagen content. Patients with these vessels usually get along quite well for many years with nothing more than a systolic hypertension. It seems, therefore, that strength is of more importance than elasticity.

The physical requirements of pliability without collapse, maintenance of integrity upon cutting, the possibility of fashioning side arms, suturability, ease of storage, availability, and reasonable cost must all be met. The homograft has the tremendous advantage of being integrated into the patient; the plastic prosthesis has the advantages of continuance of strength and ready availability. The first is partially living; the second is completely inert. Theoretically, one might suppose that a graft made of an inert, permanently strong material, which becomes at least partially viable (the viability consisting of living host tissue) might best approximate a normal vessel. Such a graft might have no inherent problems within itself, and the only problems then facing the clinician would be the quality and size of the host vessel and the sometimes relentless advancement of the original disease. One might imagine such a graft to consist of a framework of plastic of a very wide mesh, but still strong enough to prevent aneurysm formation. The interstices between the fibers should be large enough to permit easy invasion by the host, but would be initially filled by an inert, nonreactive, blood-tight, inherently strong material that is readily replaceable by the host and which, during the phase of replacement, does not involve periods of loss of strength.

DACRON-COLLAGEN GRAFT

Such a graft has been under investigation in our institution for the past 10 months. It consists of a Dacron tulle impregnated with a coating of bovine collagen and has been prepared by Ethicon, Inc. The work has been performed on mongrel dogs

which averaged 15 kilograms in weight. In each instance replacement segments were placed in the abdominal aorta. The animals were sacrificed at varying periods of time of up to 8 months.

In the hope that this work could be compared with similar experimental work performed on other materials, the literature was reviewed. However, it is almost impossible to make a direct comparison of our material with any of the others since the early chronologic achievements with these has not been specifically stated. Many of the arterial prostheses made from various plastics are well tolerated by dogs and appear to have organized well.[7, 9, 18, 22, 23, 25, 26, 28, 29] In some photomicrographs, this organization is seen to represent an ingrowth of fibrous tissue through the interstices of the prosthesis, so that a well-defined fibrous tissue lining is produced (Fig. 1). An adherent fibrous envelope surrounds the prosthesis and fibrous tissue has grown in over the anastomosis so that the prosthesis and host artery are continuous. The actual lining of the prosthesis is variously reported as being endothelial or a compressed layer of fibroblasts. Generally it has been accomplished in the dog at the end of 6 months. Shumway and associates[26] report an endothelial lining in their prosthesis at 2 months and Schumacher's[24] photomicrographs show apparently excellent organization with a nylon polythene graft in 92 days. Unfortunately, this type of response, as has been mentioned, has not been seen by us in the human being with Dacron and Teflon, and it may well be that the results given here for the new Dacron-collagen prosthesis in dogs may not be achieved in the human being. Nevertheless, the theoretical advantages of this type of prosthesis are such that we believe it advisable to present a preliminary report in the hope that further work along these lines will be stimulated. Parenthetically, it is of interest that recently Halpert[6] has theorized along these same lines, stating that the ideal prosthesis still to be found will consist of a synthetic material, the fibers of which are interspersed with absorbable hemostatic fibers woven or knitted tightly enough to prevent blood loss at the time of insertion and of sufficient porosity to allow satisfactory ingrowth of fibroblasts and endothelial cells, resulting in attachment of the prosthesis to the host tissues.

Grossly, the Dacron-collagen prosthesis shows an orderly pattern of organization at varying periods of time after insertion of the graft. The prostheses were all 5 cm. long. divided into 2 types, thick and thin, according to the amount of impregnating collagen. No significant response difference could be detected in the 2 types. However, there was a significant difference, particularly in regard to initial hemorrhage, between the untreated collagen and the collagen that had been tanned.

One week.

Gross specimen. The 1 week specimens were contained in a fibrous envelope which was not in any way adherent to the prosthesis (Fig. 2). The interstices of the graft were still occluded by the impregnating collagen and the lumen lined by a red, granular coagulum.

Microscopic section. Sections of the proximal portion showed an artefactual separation of the Dacron prosthesis from the surrounding fibroadipose tissue (Fig. 3).

The fibroadipose tissue showed active fibroplasia and a minimal inflammatory infiltrate comprised of polymorphonuclear leukocytes, a few lymphocytes, and some plasma cells. The prosthesis itself showed the open meshwork with the interstices filled

Fig. 2. One-week gross specimen.

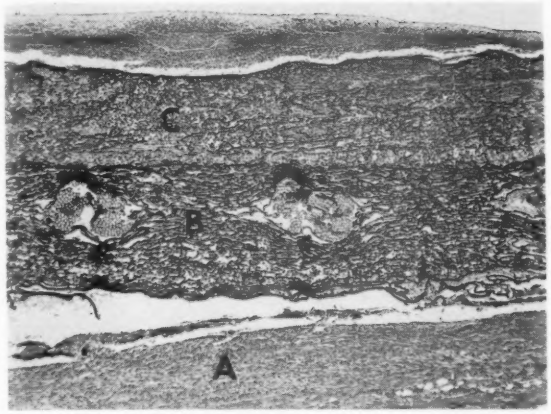

Fig. 3. One-week microscopic section. *A,* Fibroadipose tissue. *B,* The prosthesis. *C,* Fibrin clot covering surface of prosthesis.

by a series of haphazardly arranged, tangled fibrils of bovine collagen with irregular interstices containing small numbers of erythrocytes. The surface of the prosthesis was covered by fibrin clot containing a few histiocytes, erythrocytes, and neutrophils. There was no tonguelike extension of fibroplasia extending from the severed end of the aorta out into the graft, although there was a focal zone of reactive hyperplasia with capillaries and occasional inflammatory elements present at the anastomotic line. The lining consisted of a thin fibrin layer, maximally 1 mm. in thickness.

Two weeks.

Gross specimen. By 2 weeks the fibrous envelope was partially adherent but could be readily dissected free by lysis of delicate fibrous and fibrinous bands (Fig. 4). The wall of the prosthesis and the lining were similar to those of the 1-week specimen.

Microscopic section. The 2-week specimen showed a lack of inflammatory reaction similar to that in the specimen at 1 week (Fig. 5). The zone of fibrosis and fibroplasia in the fibroadipose tissue adjoining the prosthesis was more mature but, as yet, there had been no extension of fibroblasts into the prosthesis except at microscopic points. At the anastomosis a well-developed zone of fibroplasia extended across the anastomotic line onto the surface of the prosthesis and this tongue, in turn, was covered in part by endothelium. The prosthesis itself appeared quite similar to the 1-week specimen. The impregnating collagen appeared well retained. The lining surface of the prosthesis now appeared to be of more dense fibrin with enmeshed erythrocytes and was somewhat thinner than the fibrin lining of the 1-week specimen.

Three weeks.

Gross specimen. At 3 weeks the fibrous envelope was more adherent than earlier, but still could be separated by forceful dissection. The lining was smoother and averaged approximately 1 mm. in thickness.

Microscopic section. The peripheral enveloping zone of fibrosis was wider than previously and there was extension of fibroblasts into the interstices of the prosthesis at numerous points. Foreign-body reaction to the Dacron of the prosthesis was present but still remained minimal. The inflammatory reaction was largely composed of histiocytes containing hemosiderin, plasma cells, and lymphocytes. A mural fibrin thrombus was present and was focally organized, particularly at the anastomotic line. This organization was part of the tongue of advancing fibroblasts.

Four weeks.

Gross specimen. The 4-week specimen was firmly adherent to the fibrous envelope (Fig. 6). A thin, semitransparent membrane covered the anastomotic lines.

Microscopic section. A dense surrounding fibrous envelope of mature collagenous connective tissue stained bright green in a Masson trichrome stain. The prosthesis adhered densely to this envelope and there were irregular extensions of this material into the

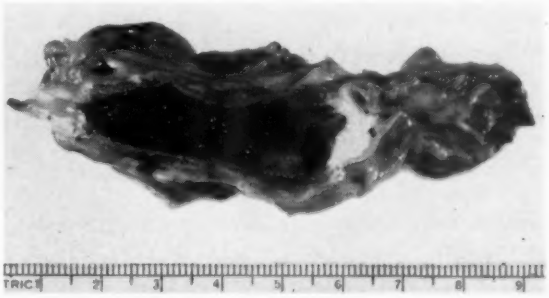

Fig. 4. Two-week gross specimen.

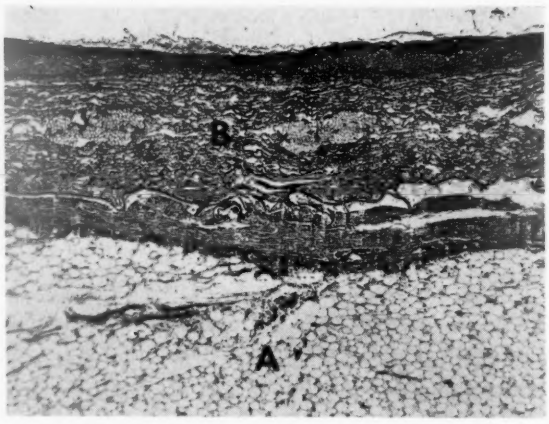

Fig. 5. Two-week microscopic section. *A*, Fibroadipose tissue. *B*, The prosthesis.

Fig. 6. Four-week gross specimen.

interstitial areas of the prosthesis, most particularly between the Dacron meshwork (Fig. 7). The interstices of the bovine collagen were now partially filled with green-staining collagenous connective tissue from the host. Inflammatory reaction was meager. The lining of the prosthesis consisted of a zone of fibrous tissue apparently covered by endothelium that ranged in thickness from about 1 mm. to less than 0.1 mm., being thinnest in the more central extent. This lining was continuous with the lining of the dog's aorta.

Five weeks.

Gross specimen. The 5-week specimen was essentially the same as the 4-week specimen.

Microscopic section. The appearance was substantially the same as that of the 4-week specimen, although there was slightly less of the bovine collagen remaining and more of green-staining collagen contributed by the host, particularly at the anastomosis.

Two and one-half months.

Gross specimen. The organization was almost complete. The fibrous envelope was firmly adherent and the lumen lined by a thin, well-defined, smooth, semitransparent, grayish membrane.

Microscopic section. There was notable progress of the fibrous-tissue ingrowth into the prosthesis. Only an occasional, longitudinally oriented wavy thread of the original prosthetic impregnation remained.

Eight months.

Gross specimen. The prosthesis was solidly united to the fibrous envelope (Fig. 8). In cross section, the entire thickness of the prosthetic wall was slightly less than 2 mm. The lumen was covered by a smooth, glistening, grayish membrane that appeared continuous with the intima of the host artery.

Microscopic section. The prosthesis was completely organized by mature collagen that filled all of the interstices and had replaced all but a few of the original bovine collagen fibrils (Fig. 9). The luminal aspect of the prosthesis was smooth and continuous with the dog's aorta. There was virtually no inflammatory reaction. The Dacron material of the prosthetic meshwork appeared embedded in a continuous, rather uniform collagen mass. Externally, the prosthesis blended with the adjoining fibroadipose tissue.

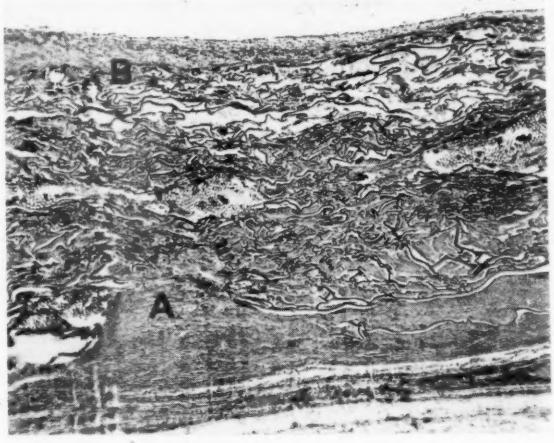

Fig. 7. Four-week microscopic section. *A*, Dense surrounding envelope of mature collagenous connective tissue. *B*, Fibrous tissue apparently covered by endothelium which lines the prosthesis.

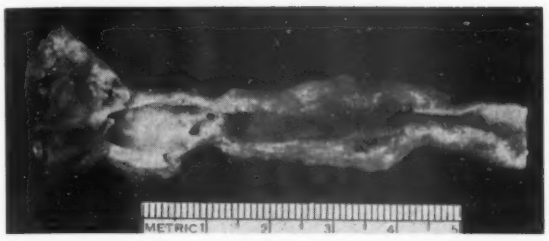

Fig. 8. Eight-month gross specimen.

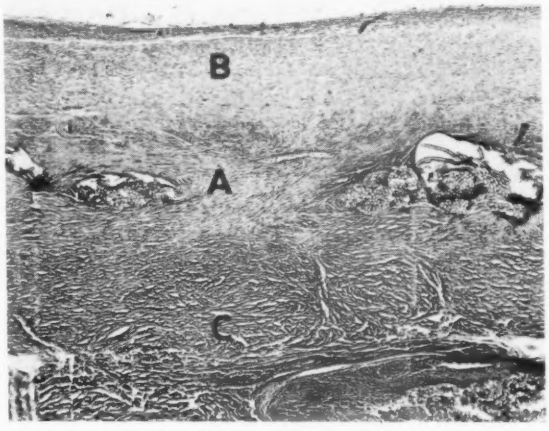

Fig. 9. Eight-month microscopic section. *A,* Mature collagen which fills all of the interstices. *B,* Smooth luminal aspect of prosthesis. *C,* Adjoining fibroadipose tissue which blends into prosthesis.

COMMENT

Our early enthusiasm for the Dacron-collagen graft is tempered by the knowledge that the results of work in the experimental animal are not necessarily the results to be obtained in the human being. However, we believe that the concept of a graft that is not protein, nor yet all plastic, but which retains the better elements of both substances and that encourages the eventual replacement of most of the graft by the host's own living tissue may offer a key to better arterial surgery in the future.

REFERENCES

1. Barnett, W. O.: Experimental nylon aortic substitutes, A. M. A. Arch. Surg. **76:** 1, 1958.
2. Burton, A. C.: Relation of structure to function of the tissues of the wall of blood vessels, Physiol. Rev. **34:** 619, 1954.
3. Denman, F. R., Brown, W. G., Skinner, S. J., Fitch, E. A., and Glass, H. G.: Fate of human aortic homografts—ten, twenty-four, and twenty-seven months after transplantation, A. M. A. Arch. Surg. **76:** 944, 1958.
4. Egdahl, R. H.: Silicone rubber as aortic grafting material, A. M. A. Arch. Surg. **71:** 694, 1956.
5. Girvin, G. W., Wilhelm, M. C., and Merendino, K. A.: The use of Teflon fabric as arterial grafts, Am. J. Surg. **92:** 240, 1956.
6. Halpert, B., De Bakey, M. E., Jordan, G. L., Jr., and Henly, W. S.: The fate of homografts and prostheses of the human aorta, Surg. Gynec. & Obst. **111:** 659, 1960.
7. Harris, E. J., Schumacker, H. B., Jr., Siderys, H., Moore, T. C., and Grice, P. F.: Pliable plastic aortic grafts: experimental comparison of a number of materials, A. M. A. Arch. Surg. **71:** 449, 1955.
8. Harrison, J. H.: Limitation to knitted synthetic tubes as vascular prostheses, A. M. A. Arch. Surg. **74:** 557, 1957.
9. Harrison, J. H.: Personal communication, 1961.
10. Harrison, J. H.: Synthetic materials as vascular prostheses. I. A comparative study in small vessels of nylon, Dacron, Orlon, Ivalon sponge and Teflon, Am. J. Surg. **95:** 3, 1958.
11. Harrison, J. H.: Synthetic materials as vascular prostheses. II. A comparative study of nylon, Dacron, Orlon, Ivalon sponge and Teflon in large blood vessels with tensile strength studies, Am. J. Surg. **95:** 16, 1958.
12. Harrison, J. H., and Adler, R. A.: Nylon as a vascular prosthesis in experimental animals with tensile strength studies, Surg. Gynec. & Obst. **103:** 613, 1956.
13. Hass, G. M.: Elastic tissue: study of elasticity and tensile strength of elastic tissue isolated from human aorta, Arch. Path. **34:** 971, 1942.
14. Kittle, F., and Taquechel, C.: A preliminary investigation of dermal heterografts (leather) as vascular prostheses for vascular defects, A. M. A. Arch. Surg. **74:** 96, 1957.
15. Krafka, J., Jr.: Comparative study of histophysics of the aorta, Am. J. Physiol. **125:** 1, 1939.
16. Newton, W. T., Weichselbaum, T. E., and Butcher, H. R.: Equine arterial heterografts altered by controlled enzymatic digestion, A. M. A. Arch. Surg. **73:** 432, 1956.
17. Ouzounian, G. S.: Arterial grafting with yardgoods, nylon cloth, A. M. A. Arch. Surg. **73:** 192, 1956.
18. Poppe, J. C., Miller, D., and Thatcher, B.: Selection and preparation of fabric for blood vessel grafts, Am. J. Surg. **92:** 248, 1956.
19. Pratt, G. H.: Replacement arterial grafts, A. M. A. Arch. Surg. **76:** 271, 1958.

20. Rosenberg, N., Henderson, J., Douglas, J. F., Lord, G. H., and Gaughran, E. R. L.: The use of arterial implants prepared by enzymatic modification of arterial heterografts, A. M. A. Arch. Surg. **74:** 89, 1957.
21. Rosenberg, N., Henderson, J., Lord, G. H., Gaughran, E. R. L., and Douglas, J. F.: Use of enzyme-digested heterografts as segmental arterial substitutes, A. M. A. Arch. Surg. **76:** 275, 1958.
22. Sanger, P. W., Taylor, F. H., Matsuba, T., and Salomone, F.: The use of artificial fiber as an artery substitute, Ann. Surg. **143:** 862, 1956.
23. Sanger, P. W., Taylor, F. H., McCall, R. E., Duchesne, R., and Lepage, G.: Seamless Synthetic arterial grafts, J. A. M. A. **160:** 1403, 1956.
24. Schumacker, H. B., Jr., Harris, E. J., and Siderys, H.: Pliable plastic tubes as aortic substitutes, SURGERY **37:** 80, 1955.
25. Self, M. M., Cooley, D. A., De Bakey, M. E., and Creech, O., Jr.: The use of braided nylon tubes for aortic replacement, Ann. Surg. **142:** 836, 1955.
26. Shumway, N. E., Gliedman, M. L., and Lewis, F. J.: Experimental study of the use of polyvinyl sponge for aortic grafts, Surg. Gynec. & Obst. **100:** 703, 1955.
27. Voorhees, A. B., Jr., Jaretzki, A., III, and Blakemore, A. H.: Use of tubes constructed from Vinyon "N" cloth in bridging arterial defects: preliminary report, Ann. Surg. **135:** 332, 1952.
28. Wesolowski, S. A., and Sauvage, L. R.: Comparison of the fate of Orlon mesh prosthetic replacement of the thoracic aorta and aortic bifurcation, Ann. Surg. **143:** 65, 1956.
29. Whittlesey, R. H., Sekerak, N. W., Blunt, J. W., and Hudack, S. S.: Observations of elastic synthetic fabric sleeves as vascular prostheses, A. M. A. Arch. Surg. **73:** 440, 1956.

The vascular pattern of intestinal villi in rats after partial gastrectomy

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The gastrointestinal function after partial gastrectomy—either by the technique of bringing the gastric remnant into continuity with the duodenum (Billroth I) or by creation of an upper jejunal loop (Billroth II)—has been a frequent subject of experimental as well as clinical investigation. Recent literature on this topic has been thoroughly reviewed and critically evaluated by several Scandinavian authors.[1, 4, 8]

Today, every surgeon is aware of the fact that signs of nutritional disorder (loss of weight, anemia, sideropenia, avitaminosis, and so forth) often appear after gastric resections. Since various manifestations of malnutrition are found also in the presence of a normal caloric intake, metabolic studies have been focused on other possible causes such as increased intestinal motility and defective digestion and/or absorption. Recenty a critical analysis of some of these postoperative complications has been presented.[4]

The particular intestinal function of absorption is intimately linked with the capillary blood flow in the vascular unit of the intestinal villus. If the arterial blood flow is directed away from this capillary area and is shunted directly into the veins, the functional capacity of the intestinal villus is completely eliminated as to its contribution to the passage of water and nutrient solutes from the intestinal lumen into the blood stream.

During recent years the vascular microanatomy of the gastrointestinal wall has been a subject of primary research in our laboratory. Using the rat, we have been able to visualize microangiographically the arteriovenous anastomoses in the intestinal villi of an isolated jejunal loop. These arteriovenous communications were essentially the same as those previously demonstrated by us in the gastric mucosa after vagotomy.[6, 7] The arterial component was a precapillary vessel. We previously proposed the term "arcade arteries" to describe these 2 precapillary vessels which ordinarily supply the dense capillary network of the intestinal villus. The drainage of the anastomosis was via the main venous components of the villus.

In consideration of the nutritional disorders which follow gastric resections, we have thought it perhaps applicable to analyze microangiographically the vascular and especially the capillary patterns of the intestinal villus in rats after Billroth I and II resections. To facilitate a comparative analysis, experimental studies of this type were conducted on animals with an operative anastomosis between the intact stomach and an upper loop of the jejunum.

MATERIAL AND METHODS

Fifteen white laboratory rats which weighed initially 200 to 280 grams were used. With open ether anesthesia gastric resections were performed which invariably sacrificed two-thirds of the secretory part of the rat stomach. Gastrointestinal continuity was restored by anastomosis of the gas-

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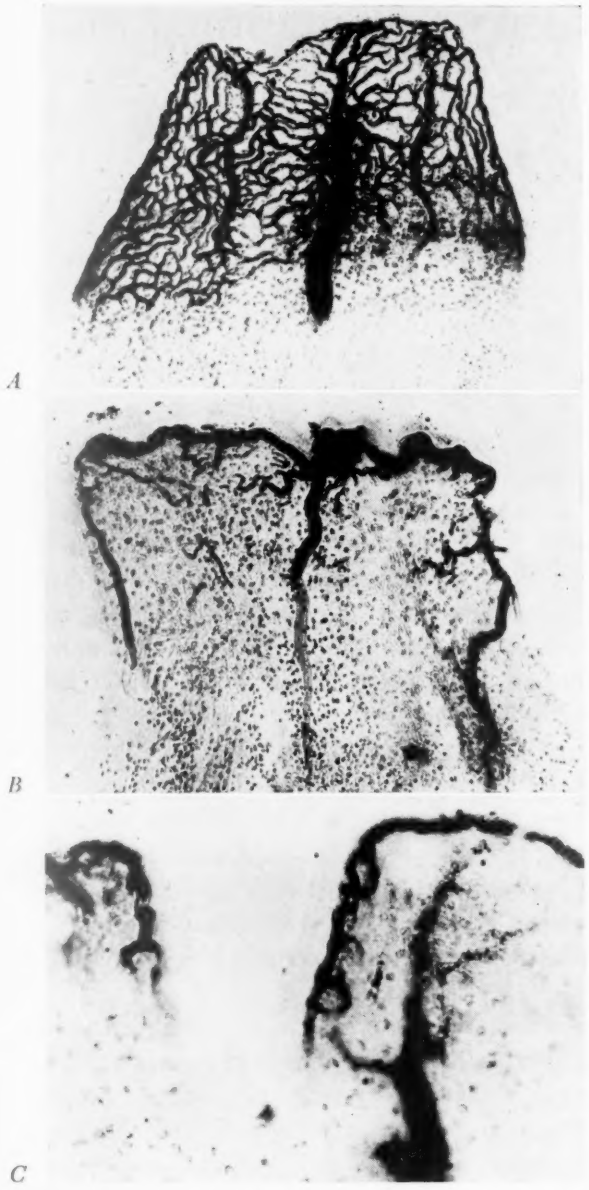

Fig. 1. *A,* Completely normal vascular unit of duodenal villus. *B,* Duodenal villus from region of anastomosis (Billroth I). Note the complete blocking of the capillary area. The central artery divides in the shape of a T into the arcade arteries. *C,* Detail of such a villus which shows the precapillary arcade artery draining directly into the stem vein.

tric remnant with the duodenum (Billroth I group) or an upper jejunal loop (Billroth II group). In every case one-third of the transverse section of the gastric remnant corresponding to the greater curvature was used to accomplish the gastrointestinal anastomosis. The Billroth I and II groups were represented by 5 animals, respectively. A simple gastroenterostomy was performed in 5 additional rats. The diameter of the anastomosis and the level of the jejunal loop corresponded to those in the rats of the Billroth II group.

During the first 2 or 3 postoperative days the animals received 15 ml. of physiologic salt solution daily by subcutaneous injection. Water and food were allowed orally beginning on the fourth postoperative day.

The immediate postoperative course was often complicated and the mortality rate considerable. The most frequent cause of death was leakage from the anastomotic site. The 15 animals included in this study, however, experienced uneventful recoveries during the experimental period of 4 to 8 weeks.

Laparotomy was then performed under open ether anesthesia. The anatomy of the operating field was carefully surveyed with special attention to the gastrointestinal anastomosis. Satisfactory integrity of the gastrointestinal anastomosis was present in all cases.

Microangiography was then performed according to the principles previously recommended by us which included a hemoglobin staining method.[5] For this purpose representative sections of the small intestinal wall were always taken from the same area of the duodenum and the jejunum, including the gastrointestinal anastomoses. For a detailed description of the technique used to visualize the vascular system of isolated intestinal villi, the reader is referred to the aforementioned paper.

OBSERVATIONS

Billroth I group. Intestinal villi were completely devoid of capillary vessels at the site of the anastomosis as well as in the proximal part of the duodenum. The striking difference between the normal vascular pattern of duodenal villi, dominated by the finely meshed capillary net, and that of duodenal villi obtained from these experimental animals is evident from Fig. 1. The central artery is clearly seen in the empty villus running upward to the subepithelial re-

gion. No branches are given off during its course through the villus, although it terminates in a T-shape and gives rise to the 2 arcade arteries. A capillary net is not visualized and the precapillary arcade arteries eventually drain into the stem veins of the villus. This vascular picture corresponds to that of an arteriovenous anastomosis established by a precapillary artery and a stem vein.

Distalward, the capillary area of the duodenal villi gradually opens. At upper levels of the section there is a sparse anastomosing and the capillary net is of wider mesh as illustrated by Fig. 2. Approaching the duodenojejunal flexure, the capillary area becomes more nearly normal. In the jejunum the vascular pattern of intestinal villi is completely normal (Fig. 3).

Billroth II group. In the proximally closed duodenal loop intestinal villi have a rather normal vascular pattern. There is a minimal reduction of the capillary network in contrast to the almost nonexistant capillary arrangement in the Billroth I group (Fig. 4). The jejunal section of the gastrojejunal anastomosis demonstrates intestinal villi with good capillary visualization even though there is a definite quantitative reduction of the capillary unit. The relative sparseness of anastomoses between the capillary vessels is a characteristic feature. The capillaries derived from the arcade arteries divide in a fan shape and empty into the stem vein (Fig. 4). More distally the vascular pattern of the jejunal villi becomes quite normal with a dense capillary system filling the villus.

Gastroenterostomy group. Intestinal villi from the duodenum, the afferent and efferent jejunal loops, and the jejunal section of the gastrojejunal anastomosis had vascular units of normal appearance. At every level of the small intestine thus investigated the capillary area was completely outlined as a finely meshed net dominating the vascular architecture of the villus. No deviation from the normal, either qualitative or quantitative, could be observed. This is fully demonstrated in Fig. 5.

DISCUSSION

After gastric resection with Billroth I anastomosis some significant circulatory changes could be visualized microangiographically. In intestinal villi from the proximal half of the duodenum it was possible to demonstrate a complete blocking of the capillary area. The arterial blood was accordingly shunted directly into the stem veins without entering the capillary bed. A capillary area of normal extent and density was gradually encountered in the distal por-

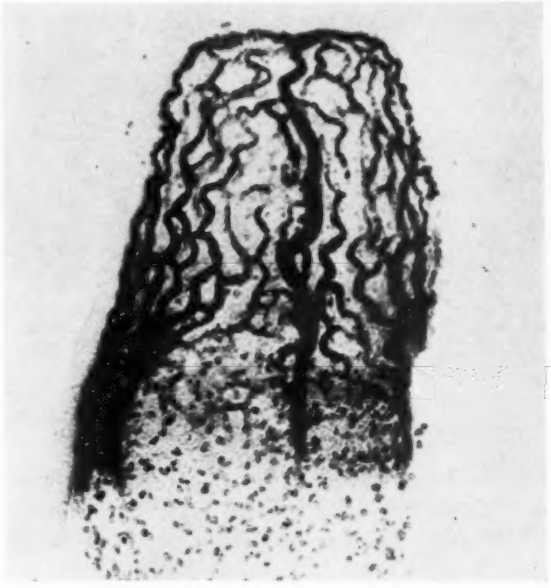

Fig. 2. Villus from distal portion of the duodenum (Billroth I). The capillary unit is relatively sparse.

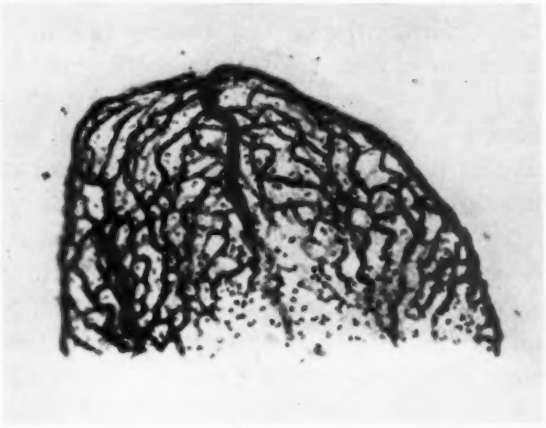

Fig. 3. Jejunal villus (Billroth I) with normal density of capillary pattern.

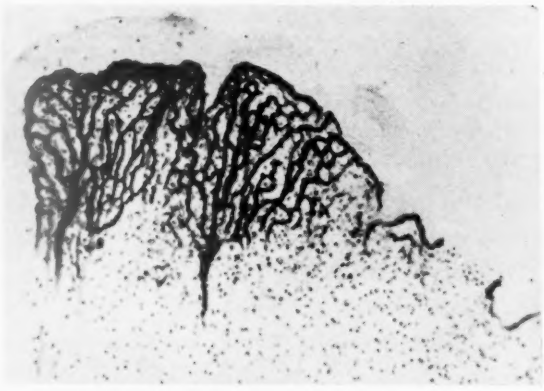

Fig. 4. Jejunal villus from region of anastomosis (Billroth II) showing somewhat reduced capillary area. The capillaries are seen to converge toward the stem veins in a fan shape.

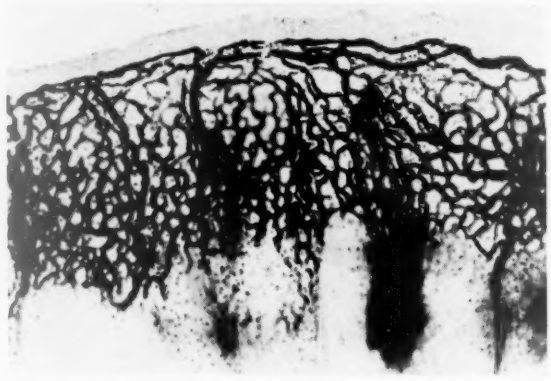

Fig. 5. Jejunal villus from region of anastomosis (gastroenterostomy). A dense capillary pattern is visualized.

tions of the duodenum. These findings are in obvious contrast to the sparsely reduced capillary unit found in the duodenal and, in particular, the jejunal villi from animals operated upon with the Billroth II technique. Furthermore, these findings and those from the Billroth I group especially are significantly different when compared to the completely normal capillary filling observed in villi from different intestinal portions of animals subjected to only gastroenterostomy.

Investigators of the nutritional disorders which follow partial gastrectomy generally agree that these complications are more frequent and pronounced after use of the Billroth II technique.[3, 4, 8] Furthermore, it has been demonstrated conclusively that digestion as well as absorption is most active in the upper parts of the small intestine.[2]

In view of these studies, our observations appear somewhat contradictory.

The absence of capillary circulation in the intestinal villi should completely abolish the absorptive function of these structures in at least the upper half of the duodenum of the Billroth I group animals. In the Billroth II group, however, only a slight reduction of corresponding capillary filling (absorptive capacity) was noted in the duodenum and the upper jejunal loop.

In the rat, and under the given experimental conditions, it seems that the proximal half of the duodenum after Billroth I gastric resection loses much of its absorptive capacity. Its primary function might instead be one of food transport and digestion.

The absorptive activity of the upper jejunum after a Billroth II resection does not seem to be influenced by the direct flow of gastric contents. This activity might be such a predominating function of this portion of the intestine that it is not decisively altered by the changed anatomic conditions.

The results demonstrated in this experimental study with rats indicate further investigation focusing on activities such as digestion and intestinal motility. An alteration of these functions rather than of absorption might explain the nutritional disorders which follow partial gastrectomy in man.

Another point of interest suggested by the experimental observations might be discussed and, if applicable to man, may aid us in understanding the comparative frequency of recurrence of ulcers after Billroth I operations. The defective capillary circulation noted in the villi of the upper half of the duodenum should in all probability impair the mucosal nutrition in this intestinal section. This might decrease its resistance to the digestive effects of the gastric secretions.

SUMMARY

The vascular patterns of duodenal and jejunal villi have been visualized microangiographically in rats operated upon with partial gastrectomies. The gastrointestinal

continuity was restored by anastomosis of the gastric remnant to the duodenum (Billroth I group, 5 animals) and an upper jejunal loop (Billroth II group, 5 animals). To permit a comparative analysis 5 additional rats were operated upon with gastroenterostomy only (gastroenterostomy group. 5 animals).

In the Billroth I group arteriovenous anastomoses were constantly found in the intestinal villi of the proximal half of the duodenum. Accordingly, the capillary area was completely shunted off in this intestinal portion. A gradual transition to the normal occurred in the distal portion of the duodenum.

In the Billroth II group only a slight reduction of the capillary area was noted in the intestinal villi of the duodenum and especially in the jejunal section included in the anastomosis.

The gastroenterostomy group demonstrated normal capillary filling in villi obtained from all portions of the small intestine investigated.

The experimental results are briefly discussed with special reference to the nutritional disorders known to appear after gastrectomies.

A theoretical explanation is suggested for the higher tendency for anastomotic ulcer development in patients operated on according to the Billroth I technique.

REFERENCES

1. Borg, I.: Gastric flow and acidity before and after Billroth II and Billroth I for gastroduodenal ulcer, Acta chir. scandinav., suppl. 256, 1959.
2. Borgström, B., Dahlquist, A., Lund, G., and Sjövall, J.: Studies on intestinal digestion and absorption in the human, J. Clin. Invest. **36:** 1521, 1957.
3. Harkins, H. N., and Nyhus, L. M.: A comparison of the Billroth I and Billroth II procedures: clinical and experimental studies. Bull. Soc. internat. chir. **15:** 111, 1956.
4. Lund, G.: Intestinal digestion and absorption after gastrectomy, Acta chir. scandinav., suppl. 231, 1958.
5. Nylander, G., and Olerud, S.: A simple microangiographic procedure for study of the vascular pattern in the alimentary canal, Acta Soc. med. upsal. **65:** 374, 1960.
6. Nylander, G., and Olerud, S.: The vascular pattern of the gastric mucosa of the rat following vagotomy, Surg. Gynec. & Obst. **112:** 475, 1961.
7. Nylander, G., and Olerud, S.: The vascular pattern of an isolated jejunal loop—a microangiographic study in the rat, Acta chir. scandinav. **121:** 39, 1961.
8. Wallensten, S.: Results of the surgical treatment of peptic ulcer by partial gastrectomy according to Billroth I and Billroth II methods, Acta chir. scandinav., suppl. 191, 1954.

Iliac osteoclast: a new instrument which facilitates operation for exstrophy of the bladder

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Exstrophy of the bladder has attracted the interest of surgeons for many years. Recently several authors[1, 2, 3, 4] have recommended the turn-in procedure with plastic reconstruction of the urethra and abdominal wall. This can more easily be accomplished after restoration of the anatomic configuration of the infant's pelvis by bringing the greatly separated pubic bones together (Fig. 1). Bilateral iliac osteoclasis, which was first recommended by Trendelenburg[5] in 1906 and was recently emphasized by Shultz,[2] has been accepted in most centers as a routine procedure. The dotted lines in Fig. 2, *A* show the location of the osteoclasis.

Considering the difficulties which this procedure involves, I came to the conclusion that the usual available osteotomes are not very satisfactory or safe instruments for this kind of operation, even in the most experienced hands. Laceration of the superior gluteal artery has occurred with dangerous hemorrhage. Control of the bleeding is a problem because of the location of the artery in the sciatic notch and the position of the patient during the procedure. Accidental penetration of structures underlying the iliac bones may also occur.

THE INSTRUMENT

An instrument especially designed for bilateral iliac osteoclasis may help the pediatric surgeon to overcome the difficulties that have been pointed out. The instrument is actually a combination of a periosteal elevator and a lateral osteotome, so that 2 instruments are made into a single one.

The iliac osteoclast* is of stainless steel and measures 21 cm. in length (Fig. 3). The instrument consists of a head and handle united at an angle of 130 degrees. This angulation facilitates the cutting of the iliac bone without exertion of significant pressure on the underlying exstrophic bladder.

The tip of the head acts as a periosteal elevator and pushes the strip of periosteum

*The instrument is manufactured by the V. Mueller and Company, 320 South Honore Street, Chicago 12, Ill.

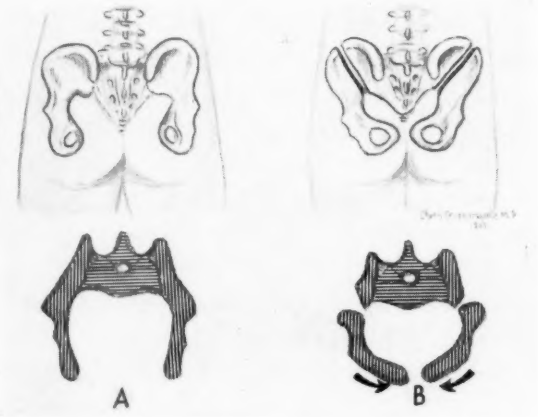

Fig. 1. Semischematic drawing of the pelvis of an infant with exstrophy of the bladder. *A,* Note the greatly separated pubic bones. *B,* The pubic bones have been approximated after bilateral iliac osteoclasis.

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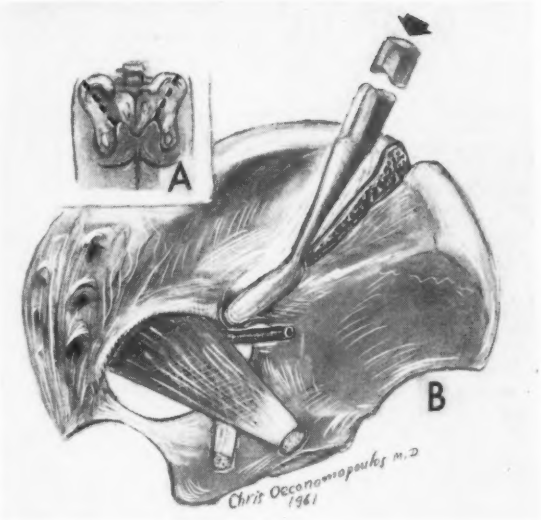

Fig. 2. An outline of the iliac osteoclasis. *A*, The dotted lines indicate the location of the osteoclasis. *B*, The instrument elevating the periosteum which then acts as a protector of the superior gluteal artery when the bone is subsequently cut.

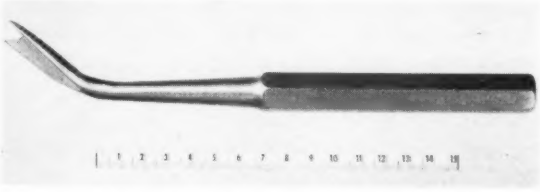

Fig. 3. View of the iliac osteoclast for infants.

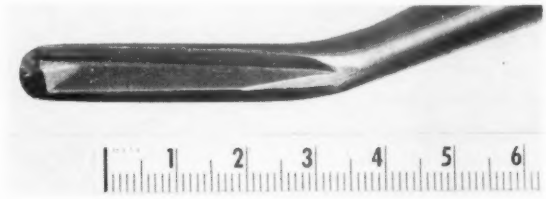

Fig. 4. Close-up of the head of the instrument.

which protects the superior gluteal artery, while the lower tip cuts the iliac bone completely (Fig. 2, *B*). The cutting edge of the head is 8 mm. in depth. This size is adequate for complete division of the iliac bone in children from 2 weeks to 3 years of age. This figure was obtained after measurements of the thickness of the iliac bone in 20 infants at autopsy.

An important feature of the instrument is the protective edge which does not permit accidental penetration and injury to the underlying structures (Fig. 4).

The iliac osteoclast has been tested on 11 cadavers and on 4 patients with exstrophy of the bladder and was found effective and satisfactory.

CONCLUSIONS AND SUMMARY

Some of the practical features of the iliac osteoclast for infants are (1) simplicity of instrument–it does the work of 2 instruments with minimal injury to tissues, (2) acceleration of the operation–the procedure can be performed within 15 minutes by 2 teams simultaneously, (3) safety and suitability for small infants in whom exposure is limited, (4) elimination of the problem of injury to the superior gluteal artery, (5) protection from penetration of and accidental injury to the underlying vital structures, (6) small size, simplicity, and inexpensiveness.

REFERENCES

1. Lattimer, J. K., Dean, A. L., Jr., Dougherty, L. J., Ju, D., Ryder, C., and Uson, A.: Functional closure of the bladder in children with exstrophy: a report of twenty-eight cases, J. Urol. **83:** 647, 1960.
2. Shultz, G. W.: Plastic repair of exstrophy of bladder combined with bilateral osteotomy of ilia, J. Urol. **79:** 453, 1958.
3. Sweetser, T. H.: Plastic reconstruction for exstrophy of the urinary bladder, South. M. J. **53:** 1519, 1960.
4. Swenson, O.: Changing trends in the management of exstrophy of the bladder, SURGERY **42:** 61, 1957.
5. Trendelenburg, F.: The treatment of ectopia vesicae, Ann. Surg. **44:** 281, 1906.

Exsanguinating gastric hemorrhage in the newborn infant and observations on the "ulcer problem" in children

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Massive bleeding from the upper intestinal tract is rare in the newborn infant. Of approximately 500 cases of peptic ulcer reported in infants and children, about 10 per cent occurred in the neonatal period (1 to 14 days).[1, 2, 6] Most of the cases detected in the first year of life manifest themselves through melena, hematemesis, perforation, or obstruction.[2] The association of gastric bleeding and Ritter's disease has been reported only once previously. The child suffered hematemesis at the age of 2 days and Ritter's disease at 6 days, and died on the seventh day. Although the hematemesis persisted until the child's death, he was not operated upon.

The purpose of this paper is to investigate the cause, surgical treatment, and prognosis of gastric and duodenal hemorrhage (loosely ascribed to "peptic ulceration") and to report an interesting case pertinent to our observations.

CASE REPORT

D. F., a full-term white female infant, weighed 6 pounds, 12 ounces, at birth and was the product of a normal pregnancy and delivery. She seemed normal until she was 13 hours old, at which time she vomited 3 ounces of bright red blood. Hemoglobin concentration, determined immediately thereafter, was 23.4 Gm. per 100 ml. During the next few hours hematemesis recurred 4 times and it was decided to perform esophagoscopy. Blood clots were seen in the stomach. It was the endoscopist's impression that the bleeding did not originate in the esophagus. Shortly after this examination the hemoglobin concentration was 17.2 Gm. per 100 ml. A small French catheter was anchored and continuous nasogastric suction begun. The stomach was washed with saline solution to help determine the amount of bleeding. Frequent hemoglobin determinations showed a fall to 7 Gm. per 100 ml., at which time blood transfusion was begun. Because bleeding continued, laparotomy was performed. (At this time, at the age of 29 hours, the hemoglobin concentration was about 10 Gm. per 100 ml.) Complete examination of the large and small bowel showed the presence of blood throughout the gastrointestinal tract, although there seemed to be a particular concentration toward the stomach and duodenum. The gastric antrum was incised longitudinally and found to be full of clotted blood. This was evacuated, but a bleeding point could not be visualized. At this point a guaze pack was inserted into the distal half of the stomach, isolating it from the field. A spotlight was focused on the upper half of the stomach into which saline solution was instilled. A crimson jet could then be seen pulsating across the pool of saline solution, permitting identification of a pin-point bleeding vessel. It must be emphasized that no ulcer was seen. Without the crimson jet the entire pathologic process would have been absolutely undetectable. One suture ligature of No. 4-0 silk stopped the bleeding. The stomach was closed and a gastrostomy performed.

Convalescence was satisfactory until the second postoperative day, at which time exfoliation of the skin about the face was noted. The picture was that of a second degree burn after blistered skin has been removed. The process soon involved the trunk and extremities. A diagnosis of exfoliative dermatitis neonatorum, "Ritter's disease," was

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made. Administration of hydrocortisone, penicillin, and achromycin was begun. The baby was wrapped in gauze saturated with normal saline solution. Oral alimentation was begun on the second postoperative day. Temperature never exceeded 100.8° F. The gastrostomy tube was removed on the tenth postoperative day. Hydrocortisone and antibiotics were discontinued on the seventh postoperative day. After healing of a superficial wound infection, recovery was considered complete. The child was released from the hospital on the twenty-fifth postoperative day and has since remained well.

DISCUSSION

From 1945 to 1959, among 135,386 pediatric patients admitted at Methodist Hospital of Indianapolis (of which 81,766 were newborn) the diagnosis of peptic ulcer was made in 5 instances, not including the case we are reporting. Uncertain roentgenographic evidence was the basis of diagnosis in 4 of these. The fifth patient, age 2 months, died of hemorrhage and perforation of a duodenal ulcer proved at autopsy.

The Mayo Clinic has had about 110 cases of duodenal ulcer in infants and children, of which 92 cases were recently reported.[6] Only 3 of the patients were newborn. One infant died of gastrointestinal hemorrhage and is not included in the group of 92. The other 2 babies survived, but there is no indication as to the severity of the bleeding and "presumptive diagnosis of duodenal ulcer was made from the clinical history and physical examination—without x-ray examination." In all, 53 had no difficulty beyond the initial episode; 39 had persistent symptoms or recurrence in adult life. In 7 of 9 children operated upon (youngest 6 years), an apparently correct diagnosis had been made at least 2 years prior to operation, which perhaps indicates some reliability of diagnosis. Notwithstanding this, however, it can readily be seen that statistical analysis of the incidence of peptic ulceration in infants and children is almost impossible. The symptoms are unreliable; the roentgenographic diagnoses are often unverified. It is often difficult to make an accurate diagnosis at laparotomy,[3] and even at postmortem examination the ulcer may be difficult to detect.[2] Until diagnostic techniques are refined, therefore, we may quite possibly correctly identify only a small group of the ulcer patients and it is possible that much of the upper gastrointestinal bleeding ascribed to peptic ulcer will ultimately prove to be due to another cause.

It seems probable that the newborn infant suffering massive blood loss will deteriorate more rapidly than the adult in spite of blood transfusions. This is hypothesized on the basis of immature kidneys plus the altered levels of blood pH and electrolytes present in stored blood,[5] and the considerable difficulties of accurate estimation of blood loss. For these reasons we favor early intervention (24 to 36 hours) in cases of massive gastrointestinal bleeding in the newborn infant.

SUMMARY

1. A newborn infant with gastric hemorrhage postoperatively complicated by Ritter's disease is presented.

2. Filling part of the stomach with saline solution and looking for a "crimson jet" is a good way for the surgeon to identify the bleeding point.

3. It may be that exsanguinating gastroduodenal hemorrhage in the newborn infant should be treated operatively if it does not abate within 24 to 36 hours.

4. How often infants have peptic ulcer and the best treatment for the infant with massive gastroduodenal bleeding has not yet been determined.

REFERENCES

1. Bird, C. E., Limper, M. A., and Mayer, J. M.: Surgery in peptic ulceration of stomach and duodenum in infants and children, Ann. Surg. **114:** 526, 1941.
2. Hollander, M. H., and Stark, M. W.: Duodenal ulcer in infancy with presentation of a case, Pediatrics **6:** 676, 1950.
3. Karelitz, S., and Kahn, J. L.: Bleeding peptic ulcer, J. Pediat. **34:** 98, 1949.
4. Kendall, N., and Aegerter, E. E.: Ritter's disease, review of literature with report of a case, J. Pediat. **15:** 733, 1939.

5. McLaughlin, E. D., Nealon, T. F., Jr., and Gibbon, J. H., Jr.: Treatment of bank blood by resins, J. Thoracic Surg. **40:** 602, 1960.
6. Michener, W. M., Kennedy, R. L., and DuShane, J. W.: Duodenal ulcer in childhood, Am. J. Dis. Child. **100:** 814, 1960.
7. Williams, H., Guynn, V. L., and Reynolds, T. T.: Diagnostic procedures in bleeding of the gastrointestinal tract, S. Clin. North America, 1956.

The surgical treatment of chronic pancreatitis by pancreaticojejunostomy: an 8-year reappraisal

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In 1954, it was reported that decompression of the pancreatic duct brought symptomatic relief to selected patients with chronic pancreatitis. Although Longmire[10] and Jordan[9] have subsequently described situations in which good results were not achieved, others have substantiated the validity of the basic concept. Indeed, the scope of the original pancreaticojejunostomy, whether accomplished by a jejunal loop[14] or by caudal anastomosis,[5] has been greatly extended by the modifications introduced by Puestow,[12] Doubilet,[3] Bartlett,[1] Partington,[11] Gillesby,[8] and Carnevali.[2]

Although an earlier report reviewed our experience over the first 3 years,[7] the current reappraisal summarizes our cumulative experience with a single, unmodified operative approach, namely; caudal pancreaticojejunostomy, as used consecutively between 1953 and 1958, thus providing follow-up information for from 3 to 8 years since operation.

PATIENT MATERIAL

Twenty-eight patients have been studied. The pertinent data for all are summarized in Table I. The specific criteria by which these patients were selected for operation have been adequately described earlier.[7] Their ages varied from 26 to 53 years. All had a history of recurrent abdominal pain of from 1 to 10 years' duration (mean 4.9 years), and all but one had lost weight in amounts from 10 to 100 pounds (mean 26.9 pounds). Twenty-three (82 per cent) admitted to either current or prior excessive intake of alcohol, 8 (30 per cent) were diabetic, and 16 (57 per cent) had evidence of calcification in the pancreas. Many of the patients had disturbed personalities, generally of the psychopathic variety, including both criminal tendencies and drug addiction. None had pancreatitis as a complication of biliary tract disease, mumps, trauma, surgical operation, or other of the entities with which secondary pancreatitis has been described.

An identical clinical evaluation was conducted on all patients, including oral cholecystography and fluoroscopic examination of the upper gastrointestinal tract with barium.

At operation, 22 (78.6 per cent) had a pancreatic duct in excess of 3.0 mm. in diameter at the point of transection in the tail of the pancreas. Organic obstruction of the duct was demonstrated at the time of operation in 16 of the 20 patients so investigated (80 per cent).

All underwent resection of the distal 3 to 4 cm. of the tail of the pancreas, followed by end-to-end anastomosis of the remaining gland to a Roux Y limb of proximal jejunum in the retrocolic position. Details of the operative technique have been described elsewhere.[4]

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RESULTS

There were no operative deaths after pancreaticojejunostomy in this series. One patient (with known treatment failure) was lost to follow-up 9 months after operation and 5 others are currently not traceable, although follow-up information is available for from 2 to 4 years after their operations. One patient died 3 months after operation with diabetic acidosis incident to an abscessed tooth. Table I summarizes these data, although certain observations concerning the operation and the disease process itself seem warranted.

The operation. Decompression of the pancreatic duct by pancreaticojejunostomy was frequently successful in bringing symptomatic relief of pain. In 18 patients the relief was immediate and complete from the time of operation. In 2 others, only a single attack of pain, at 5 and seven months, respectively, interrupted an otherwise excellent course of over 4 years' duration. When failure did occur, it was readily apparent within a few months of operation in most instances, although 1 patient had been relieved of pain for 23 months before relapse. This indicates that decompression of the pancreatic duct successfully eliminated the abdominal pain in 71 per cent of the patients in this series.

The disease. Relief of pain was not necessarily of prognostic significance with regard to the course of events after pancreaticojejunostomy. Indeed, a review of the clinical

Table I. *Summary of data on 28 patients with chronic pancreatitis*

Preoperative data							*Operative findings*		*Results*			
Patient No.	*Age and sex*	*Duration (yr.)*	*Weight loss (lb.)*	*Alcoholism*	*Diabetes*	*Calcification*	*Pancreatic duct size (mm.)*	*Duct obstruction*	*Since operation*	*Last follow-up*	*Free of pain*	*Time of recurrence (mo.)*
1	40, M	1	15	+	0	+	4	+	91	82	+	—
2	45, M	9	20	+	+	+	8	+	86	78	+	—
3	37, M	1	100	+	+	+	7	+	85	69	+	—
4	33, M	1	35	+	0	+	6	+	78	38	+	—
5	53, M	2	10	+	0	0	2	+	76	61	+	—
6	28, F	6	20	0	+	0	4	+	72	3	+	—
7	35, F	6	15	0	0	+	9	+	72	63	+	—
8	46, M	5	30	+	0	+	7	+	70	55	+	—
9	26, M	5	12	+	0	0	3	+	67	57	0	23
10	41, F	4	20	0	+	+	7	+	65	63	0	12
11	52, M	2	30	0	0	0	3	0	64	32	+	—
12	31. M	7	25	+	0	0	6	?	63	48	+	—
13	39, M	10	21	+	+	+	8	+	63	32	+	—
14	39, M	5	0	+	0	0	4	+	63	54	+	—
15	31, M	3	30	+	0	0	8	+	62	47	0	3
16	36, F	9	20	+	0	+	8	?	61	52	+	—
17	36, M	8	39	+	0	+	8	+	60	24	0	1
18	44, M	8	40	+	+	+	4	+	59	53	+	—
19	44, M	4	25	+	0	0	3	0	58	25	0	13
20	39, M	7	25	+	+	+	5	0	58	39	+	—
21	36, M	4	30	+	?	+	8	+	56	19	0	3
22	28, M	2	30	+	0	0	3	0	56	54	0	2
23	29, F	7	20	+	0	0	4	?	55	40	+	—
24	38, M	6	15	+	0	0	2	?	55	9	0	7
25	32, F	8	30	+	0	+	4	?	51	39	+	—
26	27, F	1	20	+	0	0	4	?	50	36	+	—
27	46, M	5	40	+	+	+	8	?	41	36	+	—
28	50, F	1	10	0	0	+	7	?	37	36	+	—
Mean		4.9	26.9	23	8	16	5.5	16/20	63.2	51.8	20	8
Per cent				82	29.7	57		80			71.4	

Key: ? signifies information not available, + signifies present, 0 signifies absent.

Table II. *Follow-up information on 8 patients whose pain was not relieved by pancreaticojejunostomy*

	Subsequent treatment				Late complications					
Patient No.	Thoracolumbar sympathectomy	Improved	Total pancreatectomy	Improved	Diabetes	Tuberculosis	Ulcer	Jaundice	Death	Lost
9	+	0					+			
10	+	0	+	+				+		
15										+
17	+	0	+	0	+	+			+	
19	+	?								+
21	+	0			+				+	
22			+	+				+		
24	+	?								+
Totals	6	0	3	2	2	1	1	2	2	3

Table III. *Follow-up information on 20 patients relieved of pain by pancreaticojejunostomy*

Patient No.	Diabetes	Tuberculosis	Ulcer	Jaundice*	Death	Lost
1						
2		+				
3		+			+	
4	+	+				+
5						
6					+	
7						
8						
11						+
12	+			+	+	
13						+
14	+					
16						
18						
20				+	+	
23						
25						
26	+		+		+	
27						
28						
Totals	4	3	1	2	5	3

*Both patients who developed jaundice died after total pancreatectomy.

course of each patient after operation shows, with disturbing clarity, the vicious nature of this form of pancreatitis.

Table II summarizes the experience with 8 patients in whom pancreaticojejunostomy failed to relieve the abdominal pain. One refused further treatment and has since been lost to follow-up. Another subsequently underwent total pancreatectomy and is greatly improved. The remaining 6 were subjected to thoracolumbar sympathectomy. Two have since been lost to follow-up, the other 4 were not relieved. Two of these then underwent total pancreatectomy. One was improved while the other was not. In other words, the ultimate salvage rate among the 8 who failed to respond to pancreaticojejunostomy was only 25 per cent. Among the others, 2 later developed diabetes, 1 developed pulmonary tuberculosis, and 1 an active duodenal ulcer. Two of them are known to have died.

Table III summarizes the clinical course of patients who were relieved of pain by the operation. Five are known to be dead, 4 have developed diabetes (which was not

present prior to operation), and 3 have developed pulmonary tuberculosis. Two developed obstructive jaundice which mimicked carcinoma of the pancreas and required total pancreatectomy. One patient has developed an active duodenal ulcer, and another is bed-ridden with progressive peripheral vascular disease which has already required amputation of the foot. In other words, in spite of relief of pain in 20 patients who underwent pancreaticojejunostomy, only 9 are known to be living and apparently well without evidence of continued destruction of the pancreas or severe intercurrent disease.

DISCUSSION

The results observed in the carefully followed series of 28 patients seem to warrant discussion from 2 viewpoints.

First, it is apparent that operative decompression of the pancreatic duct is rewarded with success in approximately 70 per cent of selected patients with chronic pancreatitis. The improvement is manifested in 2 ways, by relief of the severe abdominal pain and by improvement in the patients' demeanor and sense of well-being. The latter are often present even when complete relief of pain is not achieved. It should be emphasized that the proper selection of patients for duct decompression requires a basic appreciation of the clinical variations of pancreatitis,[6] since neither acute pancreatitis nor recurrent acute pancreatitis would be expected to yield to pancreaticojejunostomy.

The presence of certain criteria preoperatively was of some prognostic value relative to relief of pain by pancreaticojejunostomy in this series. The most important of these were chronic alcoholism, diabetes, and calcification of the pancreas. For example, among 11 patients in whom neither diabetes nor calcification was present preoperatively, there were 5 failures (45 per cent). Meanwhile, of 10 patients in whom at least one or the other was present before operation, there were only 2 failures (10 per cent). Among patients who were diabetic, chronic alcoholics, and with pancreatic calcification, there were no failures. An analysis of the 8 patients who failed to respond to pancreaticojejunostomy showed no factors in common. Thal[13] has reported that pancreatic duct obstruction may occur at different sites and the description of multiple simultaneous points of duct obstruction by Puestow[12] may explain many failures after operations in which the duct is decompressed at a single point.

Second, our experience has greatly enhanced our appreciation of, and respect for, the ruthless impact of the disease process itself. Indeed, the overwhelming evidence in our series indicates that surgical relief of pain by no means arrests some of the other manifestations of chronic pancreatitis in the patient as a whole. Consider, for example, that in spite of a 70 per cent "success" rate in the 28 cases reviewed, 25 per cent of the patients are already dead, 21 per cent developed diabetes, 14 per cent acquired far-advanced pulmonary tuberculosis, and 18 per cent developed either severe jaundice, duodenal ulcer, or other disabling intercurrent disease.

CONCLUSIONS

1. Twenty-eight patients with chronic pancreatitis treated by caudal pancreaticojejunostomy between 1953 and 1958 have been studied.

2. Seventy per cent were relieved of the abdominal pain by this operation, and the success rate was highest in patients with the most severe forms of the disease, especially when diabetes, alcoholism, and pancreatic calcification were already present.

3. Relief of pain by pancreaticojejunostomy did not (of and by itself) protect the patient against the subsequent appearance of other manifestations of the underlying chronic disease, such as diabetes, jaundice, and tuberculosis.

REFERENCES

1. Bartlett, M. K., and Nardi, G. L.: Treatment of recurrent pancreatitis by resection inhibition and retrograde drainage of the pancreas, Ann. Surg. 152: 861, 1960.
2. Carnevali, J. F., Remine, W. H., Dockerty, M. B., Bollman, J. L., and Grindlay, J. H.:

An experimental study of side-to-side pancreaticojejunostomy after ductal obstruction, A. M. A. Arch. Surg. **80:** 774, 1960.

3. Doubilet, H.: The physiological basis for the surgical management of acute and chronic pancreatitis, S. Clin. North America **38:** 505, 1958.
4. DuVal, M. K.: Caudal pancreatico-jejunostomy for chronic pancreatitis. Operative technique, S. Clin. North America **36:** 831, 1956.
5. DuVal, M. K.: Caudal pancreatico-jejunostomy for chronic relapsing pancreatis, Ann. Surg. **140:** 775, 1954.
6. DuVal, M. K.: Chronic pancreatitis. A review, Quart. Rev. Surg. Obst. & Gynec. **16:** 77, 1959.
7. DuVal, M. K.: Pancreatico-jejunostomy for chronic pancreatitis. A reappraisal, SURGERY **41:** 1019, 1957.
8. Gillesby, W. J., and Puestow, C. B.: Surgery for chronic recurrent pancreatitis, S. Clin. North America **41:** 831, 1961.
9. Jordan, G. L., Jr., and Howard, J. M.: Caudal pancreaticojejunostomy in the management of chronic relapsing pancreatitis, SURGERY **44:** 303, 1958.
10. Longmire, W. P., Jordan, P. H., Jr., and Briggs, J. D.: Experience with resection of the pancreas in the treatment of chronic relapsing pancreatitis, Ann. Surg. **144:** 681, 1956.
11. Partington, P. F., and Rochelle, R. E.: Modified Puestow procedure for retrograde drainage of the pancreatic duct, Ann. Surg. **152:** 1037, 1960.
12. Puestow, C. B., and Gillesby, W. J.: Retrograde surgical drainage of the pancreas for chronic relapsing pancreatitis, A. M. A. Arch. Surg. **76:** 898, 1958.
13. Thal, A. P., Goott, B., and Margulis, A. R.: Sites of pancreatic duct obstruction in chronic pancreatitis, Ann. Surg. **150:** 49, 1959.
14. Tollinger, R. M., Keith, L. M., Jr., and Ellison, E. H.: Pancreatitis, New England J. Med. **251:** 497, 1954.

Surgical history

Conducted by JOHN R. PAINE, M.D.

Andreas Vesalius, surgeon

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As December 1914 approached, my friend Dr. E. C. Streeter, who had a far better collection of books than I, proposed that we call attention to the date by an exhibit of Vesaliana for the Spring meeting of the American Medical Association in Atlantic City. For this purpose we were allotted a booth and had a small pamphlet printed with a description of the books we had selected for display. It aroused little if any interest. We had arranged to alternate as showmen, Streeter in the morning hours, I in the afternoon. We met at lunch after the first morning, and on my enquiring "How did it go?" he replied, "Well, only one old codger stopped long enough to read the sign VESALIAN EXHIBIT and said, 'Got any samples?'" Streeter asked "Samples of what?" He pointed to the sign and said, "Samples of Vaseline, of course." Sadder and wiser we returned to Boston with our "samples" at the end of the week.

Harvey Cushing
A Bio-Bibliography of Andreas Vesalius, 1943

The Ionian Islands consist of jutting, sun-burnished mounds of rock which stud the blue Aegian west of Greece. It was on one of these, the Isle of Zante, that perhaps the brightest flame in medical history was extinguished on Oct. 15, 1564. So much score has been placed on the monumental work of Andreas Vesalius as the Father of Anatomy that even his most enthusiastic hierographers, such as Osler, Roth, Cushing, Fulton, and Singer, allude only in the briefest terms to his role as a practicing surgeon. Because Vesalius laid the foundations of modern medicine, perhaps no single specialty may truly claim him as its own; and yet, that he started and ended his career in the practice of surgery is incontestable.

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EARLY DAYS

Vesalius was born on Dec. 13, 1514, in the town of Brussels, a fourth generation physician of a distinguished Belgian family named Witing. His father, who served and accompanied Emperior Charles V on his journeys and campaigns, chose to call himself Andreas of Wesalia in designation of his high office. The young Andreas rebelled against this status-symbolism and became known simply as Vesalius. Trained at the University of Louvain, which he had entered at the age of 14, he manifested an early keen interest in zoology and slaked his thirst for knowledge by performing dissections on small animals. In 1533, he migrated to Paris, then the best of medical teaching centers, and had as preceptors 2 Galenist doctrinarians of great renown, Sylvius and

Guinterius. One of his fellow-prosectors was Michael Servetus, the ill-fated martyr of science. While in Paris, his ardent preoccupation with the structure and function of the body was frustrated by inept instruction and paucity of material. "My study of anatomy," he wrote later, "would never have succeeded had I, when working in Medicine at Paris, been willing that the viscera should be merely shown to me and to my fellow-students at one or another public dissection by wholly unskilled barbers, and that in the most superficial way. I had to put my own hand to the business."

He "put his hand" by surreptitiously raiding cemeteries and gibbets for bones, usually at great risk to his person. Discouraged and dissatisfied, he returned to Louvain, and in February, 1537, published his thesis, a translation and paraphrase of the ninth tome of Rhazes.

Unsatisfied and restless, he joined the Hospital at Venice, where he met Ignatius Loyola, another revolutionary figure marked for immortality. The fiery-eyed Flemish prodigy was quickly noticed. On Dec. 6, 1537, the day after he was awarded his medical degree ("with highest distinction") and when he was but 23 years of age, Andreas Vesalius was appointed by the Venetian Senate to the Chair of Surgery at the University of Padua. He was to lecture mainly on fractures and tumors, but was entrusted with the incidental added responsibility of conducting demonstrations in anatomy. Thus, initially an avocation, the latter discipline was destined to receive his all-consuming attention.

THE *TABULAE*

In 1538, Vesalius published the *Tabulae Anatomicae Sex,* a series of 6 anatomic sheets with captions simultaneously in Latin, Hebrew, and Greek. In the dedication to Narcissus Parthenopeus, Chief Physician of the Imperial Court, Vesalius explained his reasons for the plates:

> Not so long ago, most learned Narcissus, when I was chosen to lecture on Surgical Medicine at Padua, and was occupied with the treatment of inflammations, having in mind to explain the statements of the divine Hippocrates and Galen concerning revulsion and derivation, I made on a sheet of paper a hasty sketch of the veins, thinking that I might be able easily in this manner to explain what Hippocrates had meant to say. . . . You know what a tempest of dissentions and contentions this expression was the case of, even among erudite men, with regard to venesection; some say Hippocrates had meant by this expression the correct arrangement of the fibers. Others say he meant, I don't know what else. That delineation of the veins, however, proved so pleasing to all the professors and students of Medicine, that they strenuously urged me to supply a description of the arteries and nerves also. Since my teaching included the field of anatomy, I had no right to refuse them, particularly as I knew that such outlines would be of no little help to those attending dissections. . . .

The work was an overwhelming success, and was promptly pirated and counterfeited by publishers throughout Europe. It provided a more accurate depiction of anatomic structures than, for example, those drawn by Mundinus. It was deemed a visual teaching aid proffered by a naturalist, not an unorthodox pamphlet against established canons; so that the wrath of the Galenists was not excited, and there was nothing for the ecclesiastical censorship to expunge. Vesalius was in his heyday. He was much sought for lecturing, and journeyed to Pisa, Bologna, and other university cities for this purpose. In 1538, he and his former professor, Guinterius, published the *Institutiones,* a compendium of the anatomicophysiologic views of Galen, intended as a companion synopsis to the *Tabulae.*

THE *VENESECTION EPISTLE*

Vesalius' first joust with the dogmatists was an indirect product of his prefatory remarks in the *Tabulae,* as a result of which his opinion was asked on a surgical problem. A vituperative controversy already existed regarding the choice site for phlebotomy. The Arabian school had long taught that blood-letting should be "revulsive," that is, as distant as possible from the seat of disease. Pierre Brissot, a distinguished member of the Paris Faculty, had maintained in 1525 that this was in contradiction to Hippoc-

rates' instructions that blood should be drawn in a "derivative" fashion, near the sick part. Brissot was perfunctorily banished for his heresy, but the polemic he had issued was propagated with fury. With due respect to Cushing, who has labeled the whole argument "a tempest in a bleeding bowl," we must remember that disease in those days was thought to be caused by noxious humors, and that consequently the optimal region for evacuating these humors was of pressing concern. In inflammatory lesions, should bloodletting be performed in one or the other manner, depending on whether the accumulated humors were still in a state of flux, or whether they had already settled in tissues and undergone corruption? In the latter circumstance, would bleeding by "revulsion" not tend to disseminate the humors by reversing their flow? Thus, should phlebotomy by "derivation" be reserved for early stages of sickness only ("prophylactically") before the humors had become firmly anchored in some locality?

The Prince of Piedmont, a kinsman of the Emperior, died of pleuritis, and the canard was disseminated that he had been bled after the fashion of the Arabs during the agonal phase of the disease. Nicolaus Florenas, Vesalius' former professor of medicine at Louvain, requested his advice on which method of lancing was the correct one. Vesalius responded with a massive illustrated letter, dated Jan. 1, 1539, which was published in brochure form as the *Venesection Epistle*. Although he took a stand with the Hippocrates-Brissot camp, Vesalius insinuated that the raging dispute was ridiculous and irrelevant, since pleurisy occurred in a region drained by the vena cava. Mocking statements such as the following, however, served to throw his gauntlet into an arena from which he was never thereafter to extirpate himself fully:

> . . . . you know with what open variance, with what excited feelings and with what array of argument all the most learned authorities combat one another with regard to the particular vein to be opened in pleurisy—to such a degree that few doctors of any reputation can be found who have not undertaken to publish upon that subject some sample or other of their erudition, arousing against themselves very fierce rebukes from their opponents and very serious storms of ill-will. But let me pass over for the moment those argumentative persons who reject everything new, and, being eager to defend the heresy they have once imbibed, attack with the severest insults and abuse those who think a vein should be opened on the same side as that affected.
>
> I imagine that what I wrote some time ago about the Louvain doctors has not yet dropped out of your recollection. Among them was one, remarkably learned in his own opinion and self-satisfied because of his private wealth, who in a crowded assemblage was not ashamed to call Manardus, Fuchs, Curtius and Brissot the Luthers of Medicine. . . . Of course this reverend gentleman thought that those who were reclaiming Hippocrates' ancient system of healing . . . ought to be thus derided . . . while he, wise to himself alone . . . accuses them of heresy. . . .
>
> . . . if distance or nearness were the sole consideration of our discussion of cutting the elbow vein in cases of pleurisy, I should not consider it of the slightest importance whether I lanced a vein in one or the other elbow, no matter what part of the chest the inflammation attacked. Don't they then seem to you to be having a fine wrangle and to be barking like dogs at each other, while they reject that noble principle of Hippocrates regarding the alignment and continuity of the fibers? In fact, it has gone so far that in a public edict to those practising Medicine in Spain, venesection on the same side as that affected has been forbidden; for after long discussion held at Salamanca regarding this point, those who yielded complained to "the most illustrious Spanish Senate" (as you call it) that venesection on the same side causes not less harm to the human body than the Lutheran heresies to the human soul. . . .

The latter ukase was not surprising in Spain, where the dagger of the Inquisition was at the throat of all engaged in social and professional activities. Since Vesalius had inadvertently entered the fray, it might seem paradoxical that he would then consent, during 1541 and 1542, to editing the massive *Opera Galeni* being readied for publication by the famous printing firm of Giunta and Froben. Actually, this task enabled him to acquaint himself even more thoroughly with Galen's dogmas before launching his stupendous attack, in 1543, with the publication of his crowning achievement, the *Fabrica*. At the end of the intro-

duction to the *Tabulae,* Vesalius had remarked, "If I shall find this work acceptable to you and to students, some day I hope to add something greater." Few, if any, had foreseen what the "something greater" was to be, as the indefatigable Vesalius labored incessantly for 5 years in the preparation of his opus magnum.

PUBLICATION OF THE *FABRICA* AND *EPITOME*

Many consider that the *De Humani Corporis Fabrica* of Andreas Vesalius ushered in the era of modern medical science, and is the most momentous single contribution of the Christian era. In Osler's words, "The worth of a book, as of a man, must be judged by results, and so judged, the *Fabrica* is one of the great books of the world." It was to medical illustration what Da Vinci's "La Gioconda" represented to painting—an unexcelled masterpiece. In fact, the mystery of the identity of its artist has not been solved to this day. Its exquisite format and design and the creative artistry of its woodcuts have been ascribed variously to Campagnola, Vesalius himself, the celebrated Titian, or to one of his pupils, Kalkar.

The *Fabrica* was accompanied by an *Epitome* which, Vesalius explained, was "prepared as a pathway to these books and as an index of the things demonstrated in them." In other words, it was a small volume written in simpler style, and was intended to help orient readers before they sought to cope with the more advanced work. The 2 texts came as a peal of thunder heralding the Renaissance in medical science.

The Fabric of the Human Body was dedicated to Charles V. In the lengthy preface, which is partly autobiographical and gives insight into his masterful command of medicosociologic problems, Vesalius deplored the current state of decadence of the profession of surgery. He made it clear that his book was an attempt to rectify this lamentable condition by providing proper instruction to "those who practise medicine with the hands." Several passages in the introduction are indicative of this goal. The following one, of much historical interest, has seldom appeared in print:

> . . . . Although once upon a time three schools of doctors existed, namely the Logical, the Empirical and the Methodic, nevertheless the founders of these schools directed the aim of the art as a whole to the preservation of health and the elimination of diseases. In short, they referred to this end all the things which the individual men in their schools deemed necessary to their art, and they were accustomed to make use of three aids. Of these, the first was a rational plan of diet; the second, all the uses of drugs; the third, Surgery. The last shows with particular aptness that Medicine consists in the supplying of deficiencies and the removal of superfluities; and it ever stands ready for the cure of affections. Time and use have shown that, as often as we engage in medical work, Surgery is very helpful to the human race in its benefit to these affections.
>
> This three-fold scheme of doctoring was equally familiar to the doctors of each sect. The doctors themselves accommodated their own hands to curing in accordance with the nature of the affections; and they expended no less energy in training their hands than in the business of arranging the diet or of knowing and compounding drugs. For instance, over and above his other books, the volumes which the divine Hippocrates wrote on the Role of the Doctor, on the Fractures of Bones, on the Dislocations of Joints, and evils of this type—the best written of all his works—shows this clearly. . . .
>
> But no one of the ancients seems to have handed down to posterity with equal care the curing which is wrought by the hand and that which is accomplished by diet and medicines. After the devastation of the Goths particularly, when all the sciences, which had previously been so flourishing and had been properly practised, went to the dogs, the more elegant doctors at first in Italy in imitation of the ancient Romans began to be ashamed of working with their hands, and began to prescribe to their servants what operations they should perform upon the sick, and they merely stood alongside after the fashion of architects. When, soon, others also began to refuse the inconveniences of those practising true Medicine, meanwhile subtracting nothing from their profit and honor, they promptly fell away from the standards of the early doctors. They left the manner of cooking, and in fact the whole preparation, of the diet for the sick, to their attendants, and they left the composition of drugs to the vendors of medicines, and Surgery to the barbers. And so in the course of time the technique of curing was so wretchedly torn apart that the doctors, prostituting themselves under the names of "Physicians," appropriated to them-

selves simply the prescription of drugs and diets for unusual affections; but the rest of Medicine they relegated to those whom they call "Chirurgians" and deem as if they were mere servants. They shamefully reject that which is the principal and the most ancient branch of Medicine, the one which rests primarily upon the observation of Nature (if indeed it is anything else!). Yet this branch of Medicine even the kings in India practise today; and by the law of heredity in Persia they pass it all on to their children, as once the families of the Asclepiades did. The Thracians, along with many other peoples cultivate and venerate it. Although this art accomplishes absolutely nothing without the help of Nature, but rather desires to aid her as she works to free herself from disease; when a part of the art, which the Romans in times past have proscribed from the State as if designed to deceive and destroy men, has been almost wholly neglected, the result is that the utility of the art as a whole is removed and destroyed. To this primarily we owe the fact that this most sacred art is ridiculed, although many censures are normally cast at doctors anyway, since that part of the art which those educated in the liberal arts have shamefully allowed to be torn away is the part which permanently illuminates Medicine with its especial glory.

When Homer, the fount of talents, affirms that the medical man is more pre-eminent than many, and when he and the other Greek poets celebrate Podalirius and Machaon, these sons of the divine Aesculapius are not lauded because they did away with a little fever—which Nature alone cures more easily without the aid of a doctor than when the aid is applied—or because they humored the palate of men in peculiar and lamentable affections. They were celebrated because they were especially pre-eminent in the cure of hemorrhages, dislocations, fractures, contusions, wounds, and the other breaks in the continuity of the body. They freed the most noble soldiers of Agamemnon from arrow points, javelins, and other evils of this sort which are principally caused by wars and which demand the careful attention of the doctor.

But . . . I have in no manner proposed to exalt any one instrument of Medicine above the others, since the aforesaid three-fold method of help absolutely can not be disjoined and taken apart. The whole method belongs to one workman. To effect this synthesis properly, all the parts of Medicine should be constituted and prepared equally so that all the individual elements can be put to use more advantageously, and each element in turn unites all together more perfectly. . . . Therefore tyros in the art should be encouraged in all the methods, and, if it please the gods, scorning the whisperings of the "physicians," they should apply their hands likewise to curing in whatever manner the nature of the art and reason really demand, as the Greeks did. This they should do lest they turn mutilated Medicine to the destruction of the common life of man. And they must be encouraged in this more diligently in proportion as we see today that the men who are more thoroughly grounded in the art abstain from Surgery as from the plague. They are afraid that they will be traduced by the fanatics of the medical profession before the unlettered populace as "barbers." They also fear that afterwards they may not get half the profit, honor, or reputation in the eyes of either the unlearned mob or the leaders. This detestable opinion of many people in the first place keeps us from taking up the whole craft of healing; and when we arrogate to our selves only the cure of internal affections, we desire to be doctors only in a small way (to tell the truth for once!). The ensuing damage to mortals is great. . . .

One of the chapters of the *Fabrica* dealt with vivisection. In it may be found classical descriptions. There is a paragraph entitled "Examination of the recurrent nerves and the loss of voice from the cutting of them." Collapse of the lungs when the chest is punctured was discussed, together with the possibility of prolonging life for awhile by artificial respiration when the thorax is opened. That a heart which had almost stopped beating could be revived by the timely use of bellows was indicated, as well as the fact that an animal could live after removal of the spleen. Vesalius also demonstrated that it was the brain which governed motor activity of the trunk and limbs, and that the spinal cord served to relay this control.

Concerning the physiology of circulation, Vesalius might have conceivably anteceded Servetus and Harvey had he gone further than being content with casting this sarcastic barb at current dogma:

> The septum of the ventricles, composed as I have said of the thickest substance of the heart, abounds on both sides with little pits impressed in it. Of these pits, none, so far at least as can be perceived by the senses, penetrate through from the right into the left ventricle; so that we are driven to wonder at the handiwork of the Almighty, by means of which the blood sweats from the right into the left ventricle through passages which escape human vision.

The *Fabrica* was calculated to be a clarion

call freeing medicine from the fetters of Galenism, and Vesalius was unsparing in the use of vitriolic language. It was generally believed that an obscure bone in the body named "Luz" was the pivot point from which the human race was regenerated. Vesalius ground the mythical bone of Luz into dust with this acrimonious salvo:

> The dogma which asserts that man will be regenerated from this bone, of which we have just narrated the immense fiction, may be left for elucidation to those philosophers who reserve to themselves alone the right to free discussion and pronouncement on the resurrection and immortality of the soul. And even on their account we should attach no importance whatever to the miraculous and occult powers ascribed to the internal ossicle of the right great toe, however much one may be concerned about it. At our public dissections and even as an amateur, we have often obtained a better supply of these bones than those truculent male strumpets of the Venetian horde, who, to obtain the bone for purposes of comparison, as also the heart of an unpolluted male infant, lately killed a child, cut the heart from its living body, and were punished, as they richly deserved for the foulest of crimes. Moreover, this ossicle, called Albadaran by the Arabs and the truly occult and obscure philosophers alluded to, is less known to actual students of anatomy than to certain superstitious men who are capable of likening the fourth carpal bone to a chickpea.

Vesalius was also unflinching in acknowledging no authority except what his senses perceived. He dismissed Galen with acerbity, stating that his predecessor "was cheated by his monkeys in the manifold divergence of the human body from that of monkeys. He hardly noticed anything different except in the fingers and the bend at the knee."

All this was not only phenomenal audacity, coming from a 29-year-old youth, but was tantamount to overt sacrilege. In those days, the appropriate theocratic penalties for blasphemers were blazing faggots or the rack. Servetus had already been immolated at the stake. Vesalius was spared this fate, however, just as Paré was to escape the St. Bartholomew's Eve massacre, only because of royal patronage and intercession. Repercussions of other sorts, nevertheless, were not long in coming fast and furiously.

SEQUELAE OF THE *FABRICA*

Sylvius, Vesalius' former teacher at Paris, soon unleashed a tirade of vilification. His tract was entitled "A repudiation of the calumnies of a certain madman, Vaesanus, concerning Hippocratic and Galenic anatomy, by Jacobus Sylvius, the Royal Interpreter of things medical at Paris." The play on the name "Vaesanus," similar to "Vesalius," was deliberate invective, and no typographical error. "Vaesanus" is a Latin word signifying "a two-legged ass." Sylvius was appalled at the use of illustrations which went so far as to reveal unmentionable portions of the human body. After all, he argued, "Galen did not allow even plants to be depicted." He petitioned Charles V to either castigate Vesalius or have him recant:

> I implore his Majesty the Emperor to punish severely, as he deserves, this monster born and reared in his own home, this most pernicious exemplar of ignorance, ingratitude, and impiety; and to suppress him completely, lest he poison the rest of Europe with his pestilential breath. With his deadly spume, he has already infected certain Frenchmen, Germans, and Italians; but they, I believe, are ignorant of anatomy and of the other branches of Medicine. . . .

The above, multiplied severalfold, is a sample of the barrage of opposition which Vesalius faced from certain quarters until almost the closing years of his life. A brief respite from his detractors occurred with the declaration of hostilities against France in 1544. During this short-lived foray, Vesalius served in the field in the capacity of Imperial Surgeon. As in the case of many other illustrious surgeons, war supplied a proving-ground for his teachings, and honed his skill in applying them to the razor edge of experience. It also marked the end of his academic career as an anatomist.

At the Siege of Saint-Dizier, in the Marne Valley, Vesalius operated on the Prince of Orange-Chalon, who had a fatal wound of the shoulder. Outside the walls of Vitry, he treated the Lord of Aluhin and several other officers who had been mortally injured by flaming cannon-balls. By a remarkable coincidence, the Royal Physician attached to

the opposition forces was Ambroise Paré, who was rapidly gaining stature as the most ingenious surgeon in Europe. These two surgical peers, foes only through military exigency, nevertheless displayed professional gallantry. Paré introduced and popularized the *Fabrica* among the French intelligentsia by abstracting it in the vernacular. Vesalius, in turn, attempted on a certain Captain Solis disarticulation at the elbow, an operation developed originally by Paré. However, in this campaign, Vesalius still employed boiling oil, while Paré was already discarding this barbaric practice after disproving that gunshot wounds were poisonous. In September, 1544, the Peace of Crespy was signed, and Vesalius, not yet 30, returned to Court as personal physician and surgeon to the Emperor and his entourage.

VESALIUS BURNS HIS NOTES

While at Court, Vesalius also conducted postmortem examinations and embalmings on members of the nobility as a prelude to burial with pomp. His acumen in surgical pathology, then a neglected study, was brought into the open by the publication in 1546 of a series of communications under the title, *The China-Root Epistle,* after one section dealing with the use of a variety of sarsaparilla against diverse afflictions. In the very last chapter of this publication, Vesalius gave indication of the immense despondency and chagrin which had befallen him after the initial adverse reception and spoliation of the *Fabrica*. In utter disgust and anguish, he had impulsively made a sacrificial pyre of his accumulated documents!

> As to my notes, which had grown into a huge volume, they were all destroyed by me; and on the same day there similarly perished the whole of my paraphrase of the ten books of Rhazes to King Almansor, composed by me with far more care than the "Paraphrasis" which I published on the ninth book. With these also went the books of some author or other on the formula and preparation of medicines, to which I had added much matter of my own that I judged to be not without utility; and the same fate overtook all the books of Galen which I had used in learning anatomy, and which I had liberally disfigured in the usual fashion. I was on the point of leaving Italy and going to Court; those physicians of whom you know had given the Emperor and the nobles a most unfavorable report of my books and of all that is published nowadays for the promotion of study; I therefore burnt all these works mentioned, thinking at the same time it would be an easy matter to abstain from writing for the future. I have since repented more than once of my impatience, and regretted that I did not take the advice of the friends who were then with me.

WAR, AGAIN, AND THE *CONSILIA*

In the cockpit of Europe, battles were ignited for the slightest real or imagined wrong. In 1546, a civil war against the Lutheran princes of the Smalkaldic League was sparked, and flared into the conflagration that Luther had prophesied on his deathbed. Vesalius' skill in surgical operations was augmented by a wealth of material. Descriptions of his procedures have survived through the writings of eyewitnesses or professional contemporaries such as Daza Chacon and Ingrassia.

Vesalius was the first to perform a deliberate operation for osteomyelitis of the distal part of the femur, and was duly censured for this unheard-of temerity. He modified and reintroduced with success the long-abandoned Hippocratic operation of thoracentesis for empyema. He was called on to incise the foot of the Cardinal of Trent, a very particular distinction for one who had clashed with established theologic tenets. He caused an immense sensation by correctly diagnosing, and predicting the exact hour of death and autopsy findings, of the Count Maximilian of Buren, who perished as a result of an extensive mediastinal abscess from quinsy. He cured the Marquis of Velena of a chronic fistula of the chest wall ensuing from a poorly-treated empyema.

It was customary then, as now, to seek in consultation prominent surgeons for difficult cases. Written consultations, or "consilia" as they were called, were not infrequently published. Only 6 of Vesalius' *Consilia* have been preserved. The third consilium was a retort to an enquiry regarding the treatment to be employed in the case of Don Carlos of Aragon, the Duke of

Terranova, who, during a tournament, had incurred a broken rib with penetration of the left hemithorax. Vesalius' detailed description of the operation for empyema is a remarkably lucid piece of thoracic surgical literature. He quoted 4 recent instances in which he had performed the operation; 3 of the patients had recovered completely. In 1 case, he pointed out, the scapula had been perforated by the weapon, so that a different approach to the abscess had had to be employed. The fifth consilium consisted of an aggregate of letters on the surgical management of phlegmons and ulcers. In it is reported a successful operation on Chancellor Granvelle, a Knight of the Golden Fleece and the most powerful personage at Court next to the Emperor, which reveals what favor Vesalius' surgical prowess must have enjoyed.

In 1555, Charles V, who was ill of health, abdicated. He was replaced by the supercilious and insipid Philip II of Spain, whose only fame rested on his marriage to the daughter of the King of France which terminated Franco-Hispanic hostilities. The royal betrothal took place in 1559 with great éclat, including royal jousting. Henry II, the French monarch, participated in a tourney, and was struck above the right eye by a broken lance. The most important doctors of the realm were summoned immediately. In this retinue were Vesalius and the now celebrated Ambroise Paré, neither of whom was able to forestall the eventual fatal outcome. As foreseen by Vesalius, death resulted from subdural hemorrhage, the possibility of which had been discounted by the other physicians because of the absence of obvious skull fracture.

THE ROAD TO ZANTE

In 1562, the pathetic Infante Don Carlos struck the back of his head in a fall. Vesalius advised trephining, but was repulsed as a meddling alien by the royal surgeons of Spain, to which Philip had transferred his court. Instead, all sorts of religious relics and amulets, including the disintegrated corpse of a monk who had been idolized for

ANDREAE
VESSALII BRVXELLENSIS,
PHILIPPI HISPANIARVM
REGIS, MEDICI,
CHIRVRGIA MAGNA
in ſeptem libros digeſta:

In qua nihil deſiderari poteſt, quod ad perfectam, atque integram de curandis humani corporis malis, methodum pertineat.

Ab Excellen. Philoſopho, ac Medico Regio, PROSPERO BORGARVTIO, recognita, emendata, ac in lucem edita.

Forme etiam inſtrumentorum, quibus Chirurgi vtuntur, his in libris apprimè deſcripta ſunt.

Cum ampliſsimis Indicibus tùm capitum: tùm rerum omnium memorabilium.

CVM PRIVILEGIO.

VIN CENT

VENETIIS, Ex officina Valgriſiana.
M D LXIX.

Fig. 1. Title page of the original *Surgery* of Vesalius, published in 1569, 5 years after his death, by a student, Prospero Borgarutius.

his holiness, were placed on the bed of the gravely sick prince. Finally, at the insistence of Vesalius, these grisly proceedings were discontinued, and incisions were made into the scalp to evacuate considerable amounts of pus. The boy recovered, and later shed a sequestrum from the diseased bone.

Because he had unavoidably humbled the bigoted and fanatical coterie of Iberian physicians, Vesalius' life in cleric-ridden Spain was thereafter made unbearable, and he was snubbed and rebuffed at every excuse. But in other more enlightened parts of the Continent, Vesalius was gaining staunch supporters every day. The last work he authored before his death was a reply to the *Observationes Anatomicae* of Gabriel Fallopius, one of his most zealous adherents,

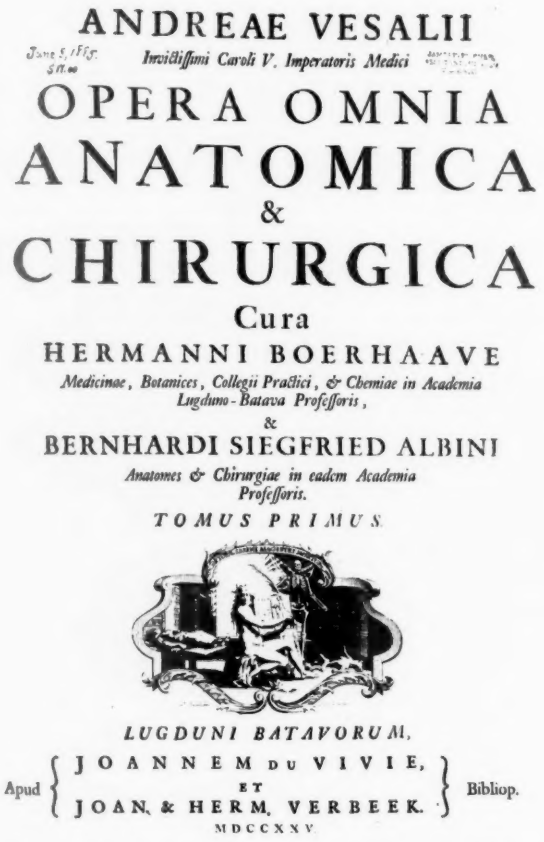
ANDREAE VESALII
Invictissimi Caroli V. Imperatoris Medici
OPERA OMNIA
ANATOMICA
&
CHIRURGICA
Cura
HERMANNI BOERHAAVE
Medicinae, Botanices, Collegii Practici, & Chemiae in Academia Lugduno-Batava Professoris,
&
BERNHARDI SIEGFRIED ALBINI
Anatomes & Chirurgiae in eadem Academia Professoris.
TOMUS PRIMUS
LUGDUNI BATAVORUM,
Apud JOANNEM DU VIVIE, ET JOAN. & HERM. VERBEEK. Bibliop.
MDCCXXV

Fig. 2. Edition of 1725 by Boerhaave, combining the *Fabrica* and *Chirurgia*. Observe the notation indicating that this 1156-page tome was purchased in 1885 for $17.00.

who made reference in his book about "the divine Vesalius." To this kindred spirit, Vesalius imparted his deep learning to be rid of the intolerable life in Spain, and to return to an academic atmosphere:

> I sincerely hope that you may long maintain this purpose in that sweet leisure of letters which is yours, and in that throng of learned men whose studies are dear to their hearts and with whom you can daily compare the concepts of your mind. For I feel that the ornaments of our art originate in that arena from which as a young man I was diverted to the mechanical practice of Medicine, to numerous wars, and to continuous travels . . . therefore continue to embellish with the fruits of your talents and industry our common school, whose memory is most dear to me.

Shortly after writing this commentary, which he was never to see in print, Vesalius left Madrid, ostensibly for a pilgrimage to the Holy Land. The circumstances of his voyage and death have been the objects of analysis and conjecture for centuries. None appears to be fully reliable, and the reader may draw his own conclusions as he sees fit from the bulky literature on this final facet of Vesalius' life. In any case, the road ended at Zante, in a lonely and unbefitting grave.

THE *CHIRURGIA*

The largest of Vesalius' surgical works was published posthumously under the heading *Chirurgia Magna in Septum Libros Digesta.* The manuscript of notes on surgery by Vesalius for a book he was apparently meditating fell into the hands of a Parisian bookseller. A student and devotee of Vesalius, one Prospero Borgarutius, obtained possession of the manuscript, appended notes which he had taken during lectures by his professor, and published the book at his own expense in 1569. There is a recital of this story in the preface, in which Borgarutius also explains rather eloquently the reasons why he keenly believed the surgical teachings of Vesalius should be preserved:

> Because of this factor it happened that after Hippocrates, Galen, Avicenna, Celsus, and many others of the same type, Andreas Vesalius of Brussels, at one time physician to the King, and a Caesarine, had shown many new things. Some of these are known. Others, because of his untimely death, would be therefore buried, unless they should be published by the industry of someone, especially one of the number that had the greatest opportunity of study with him. Since I, especially, am of this number, and since I understand that he was the personification of a kindly heart (and if anyone loves such a one let him desire his immortality), and as I have realized how much I have been forwarded by the great name of Vesalius whom I have always obeyed as if there were the power of God in this human; therefore, I have always avowed this by the immortal gods, that should the opportunity at any time offer itself to me by which I might show the incredible benevolence of that great man, I would follow him by that opportunity most diligently.

Borgarutius' gesture of gratitude was admirable; but, in his reverence for Vesalius, he seemingly deemed it unbecoming to make any changes whatsoever in the manuscript. The lack of conscientious editing, a task at

which Vesalius was expert, is glaring in the text. It is more of an uncut precious stone than the finished polished jewel. These imperfections have led some Vesalian venerators to dismiss the book as spurious, so that it has received negligible study compared to the other works. Such an a priori judgment has been, in our opinion, too hasty, because many portions of the book bear the unmistakable stamp of Vesalius. To question its authenticity would be the equivalent of rejecting the notes on surgery of John Hunter merely because they were compiled by Everard Home and others.

Fig. 3. Frontispiece of the 1725 edition is a facsimile of the one in the original *Fabrica* except for a few minor changes. The shield at the top is replaced by the Vesalian coat of arms depicting 3 weasels, a pun Vesalius employed regarding the sources of his name. The colophon at the bottom of the page has been modified to indicate inclusion of the *Chirurgia*.

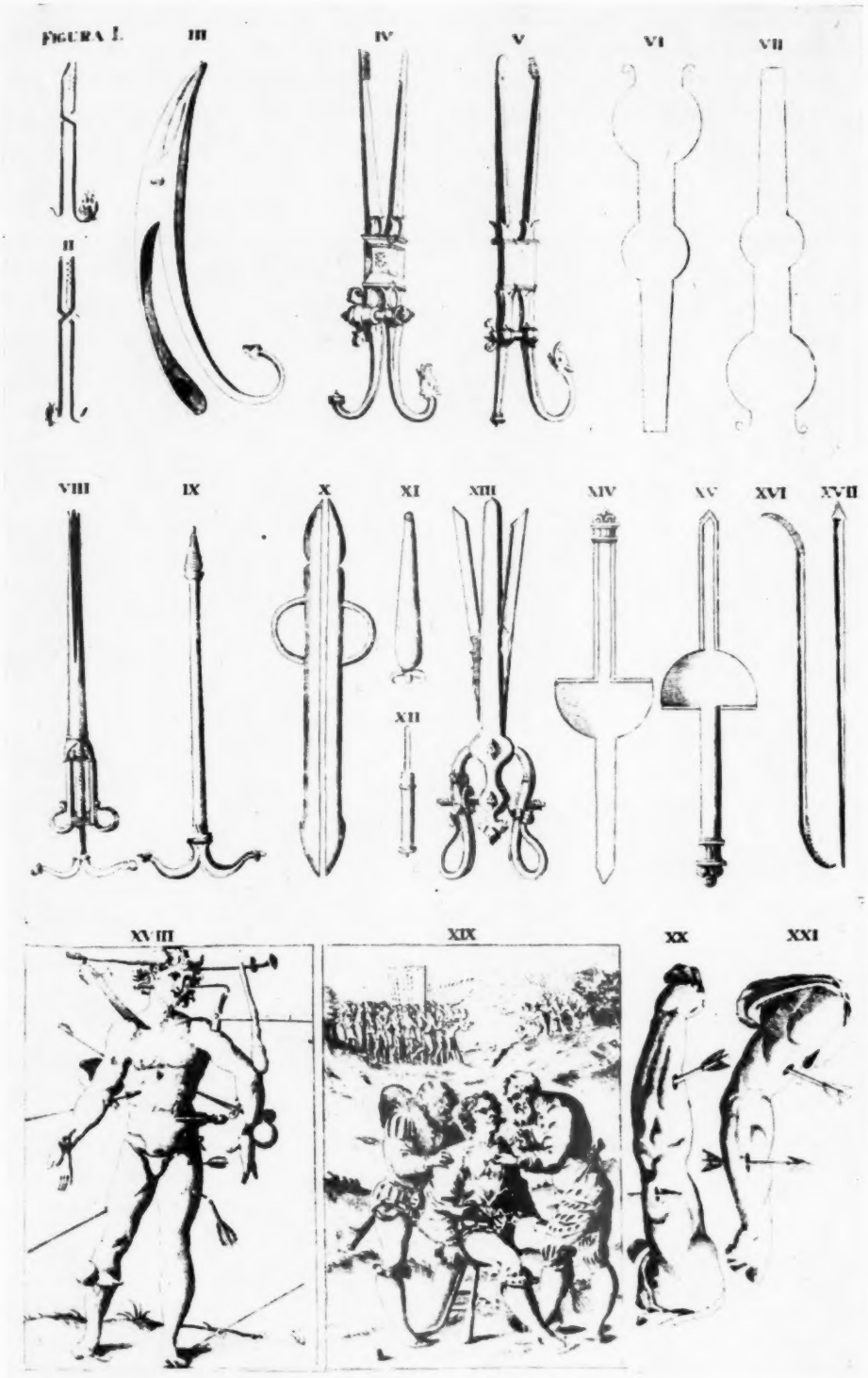

Fig. 4. Illustrations in the *Chirurgia* are reproductions from other contemporary surgical texts. Fig. XVIII is from Gerssdorff, and depicts the zodiacal "wound man." Fig. XIX, after Brunschiwig, shows extraction of a bullet ("quomodo plumbeus globus immissus extrahatur").

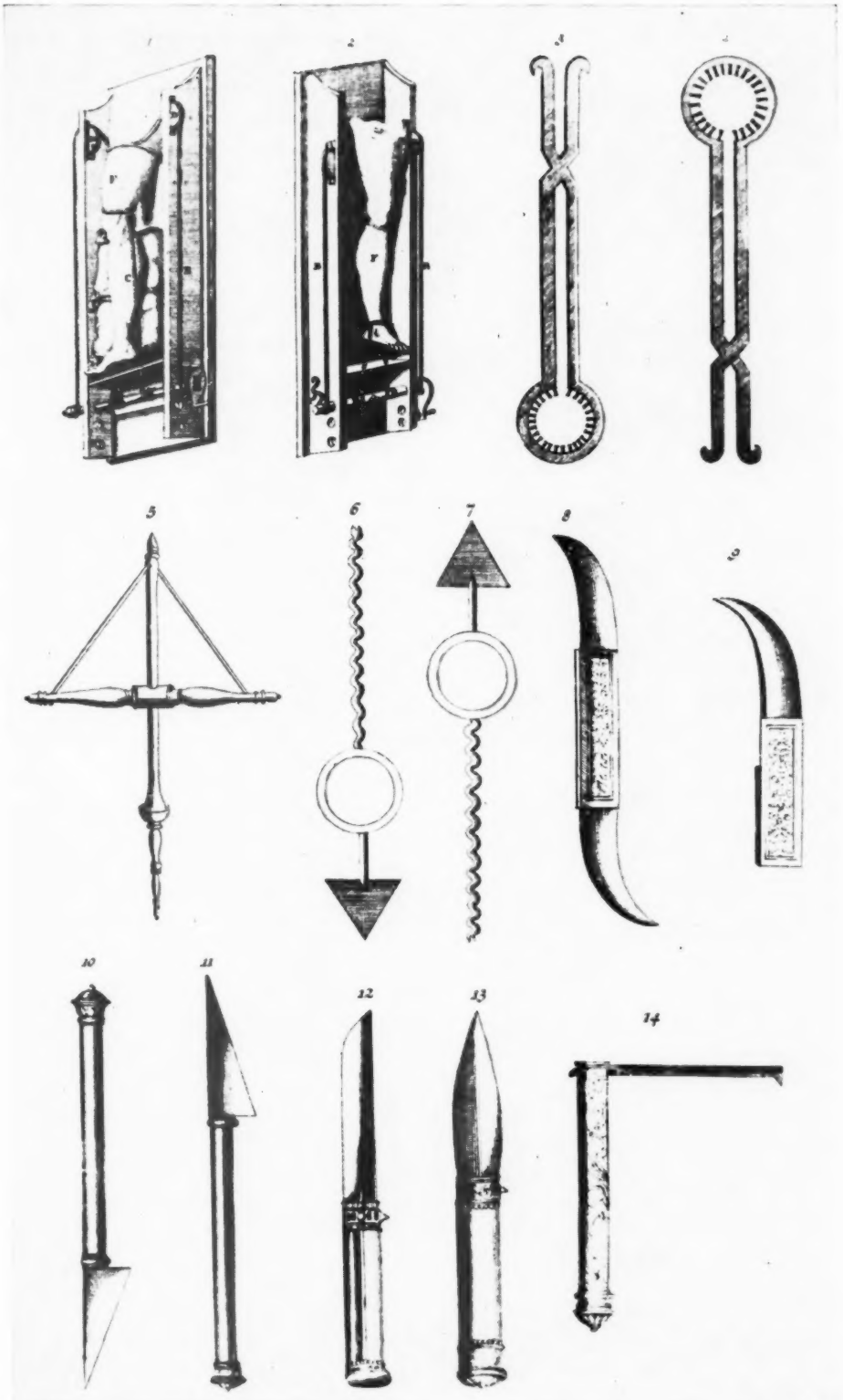

Fig. 5. More illustration replicas in the *Chirurgia*. Figs. 1 and 2 are copied from Tagault. The others show trephine apparatus, forceps, scalpels, lancets, and an instrument used for phlebotomy.

The book, 475 pages long, is divided into 7 parts, as its title indicates; first, dislocations; second, fractures; third, wounds; fourth, ulcers; fifth, neoplasms; sixth, an antidotary; and seventh, the manner of use of medicaments in surgical conditions. Before each of the surgical maladies, properly called, there is an anatomic résumé of each region. ("No anatomist, no surgeon." Vesalius was adamant on this point.) There is a paucity of illustrations, and the ones included are all facsimilies from the surgical texts of other authors. Since the printing press of Valgrisius, which produced this volume, was the same one which printed one of the editions of Tagault's *De Chirurg Institutione,* it is not surprising that the works of the 2 surgeons are typographically twin books. Of interest in the chapter on tumors is Vesalius' differentiation between "occult" and surface scirrhi, and his advocacy of surgical excision in mammary carcinoma, a truly avant-garde position at a time when the cautery was in vogue for this disease.

In the introduction to the *Chirurgia,* there is a discussion of the Art of Healing in general, its end, its means, and distinctions between the role of surgeons and that of other members of the profession. In the second chapter, Vesalius traces a portrait of the ideal surgeon, the words of which have the same cogency as when they were put on paper:

> It is necessary that the surgeon should have practised for a long time upon the cadaver; that he should be a profound observer; that he should follow the precepts of the best masters; that he should be patient and laborious; above all the friend of truth; upright and conscientious; that he should refrain from touching incurable cases which present no chance of healing; that he should be temperate, disinterested, affable, and of easy access with his colleagues; and, finally, that he should be young or of age of virile force when the hand is firm and light, the eye quick; that he should be bold and pitiless when the well-being or safety of his patient is involved.

One of the illustrations in the *Fabrica* bears the legend, "Vivitur ingenio, caetera mortis erunt" ("Genius endures. All else is mortal.") Carved in bold letters on the rock at Zante, this would be an appropriate epitaph for the great surgeon named Andreas Vesalius.

The authors are indebted to Miss Eleanor Safstorm, Chief Librarian of the Denver Medical Society, for her loan of the priceless old manuscripts employed in the preparation of this essay.

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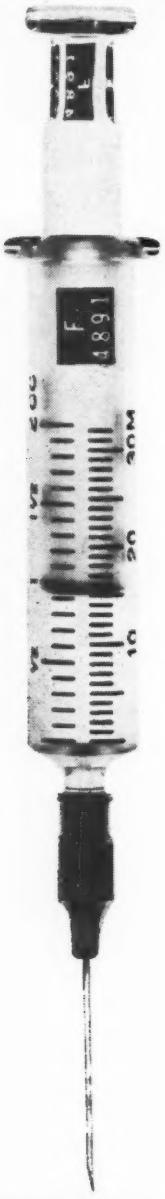

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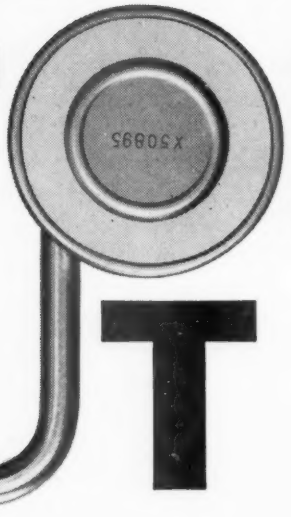

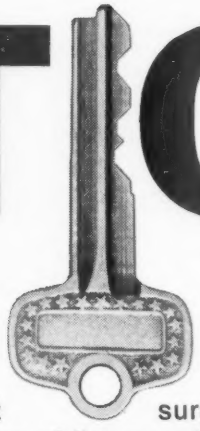

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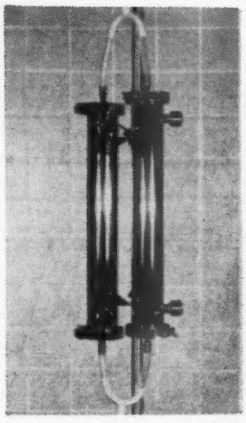

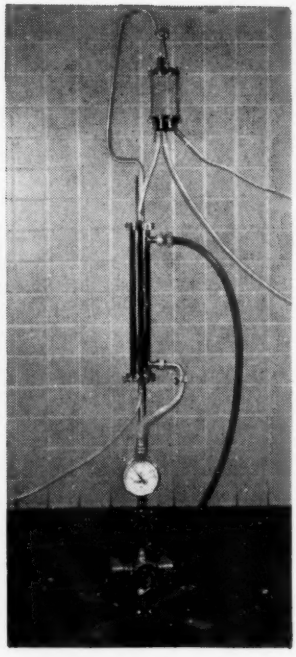

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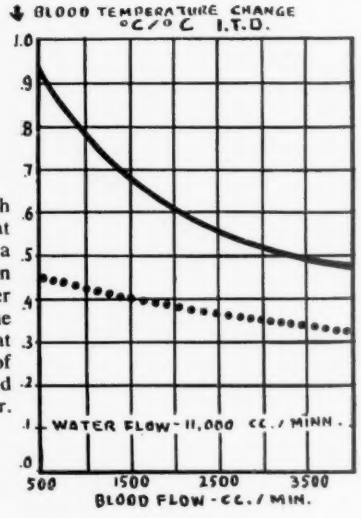

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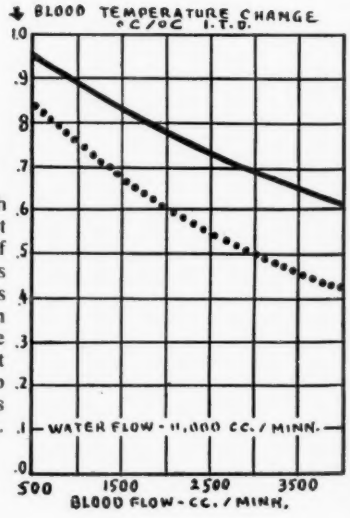

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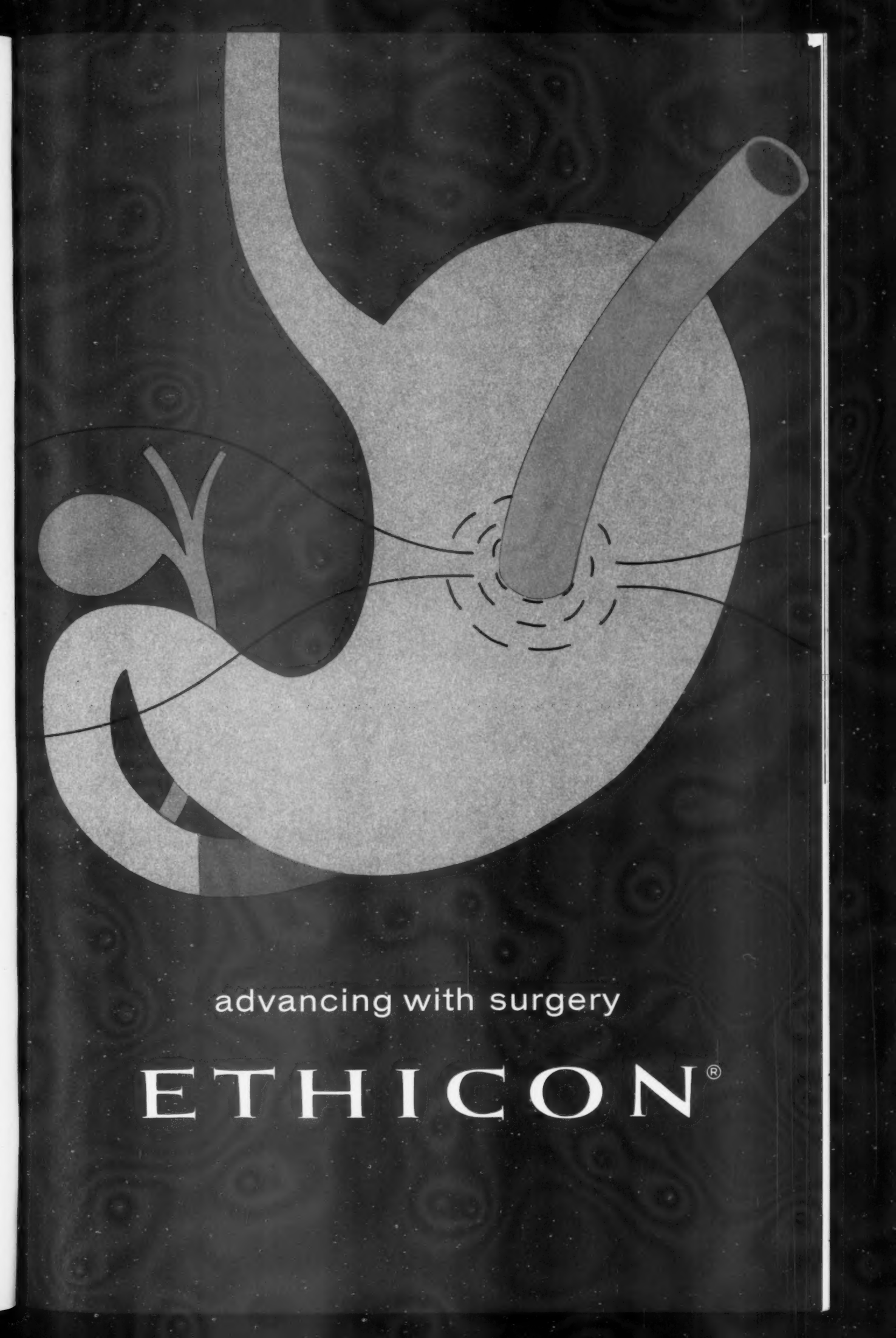
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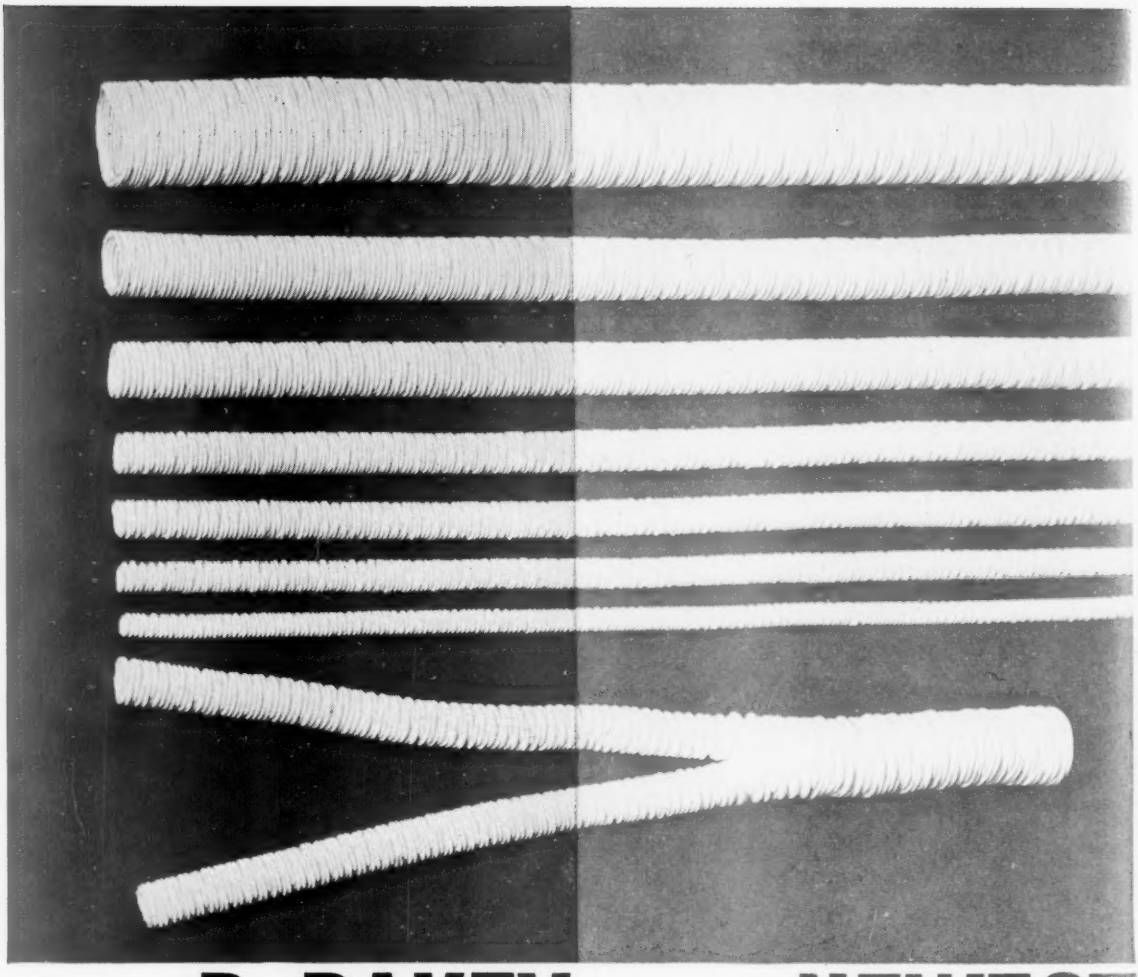

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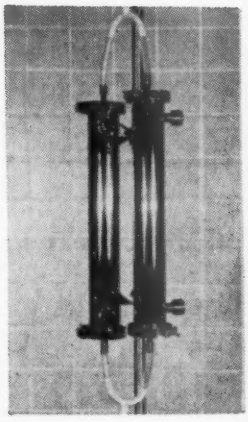

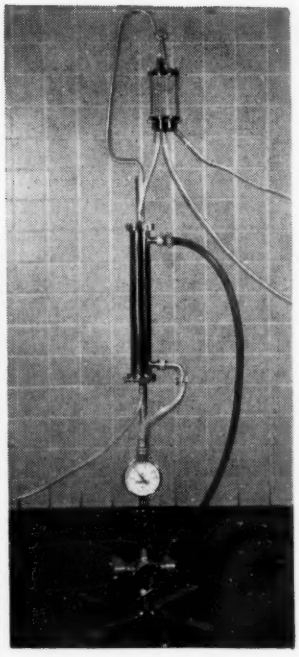

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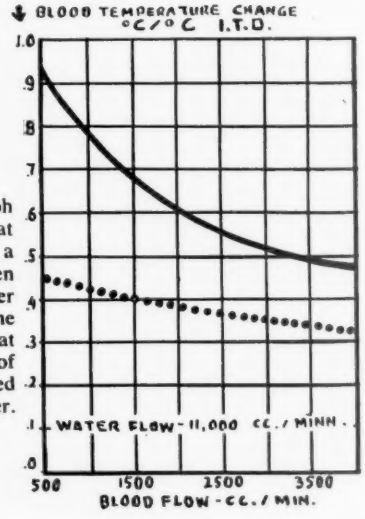

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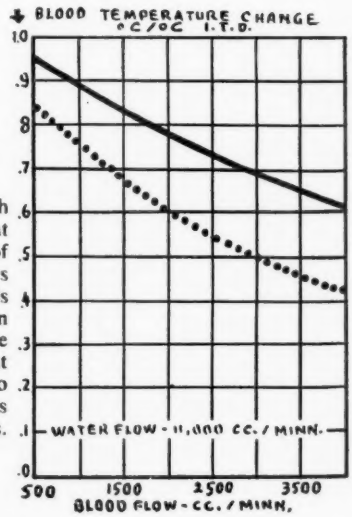

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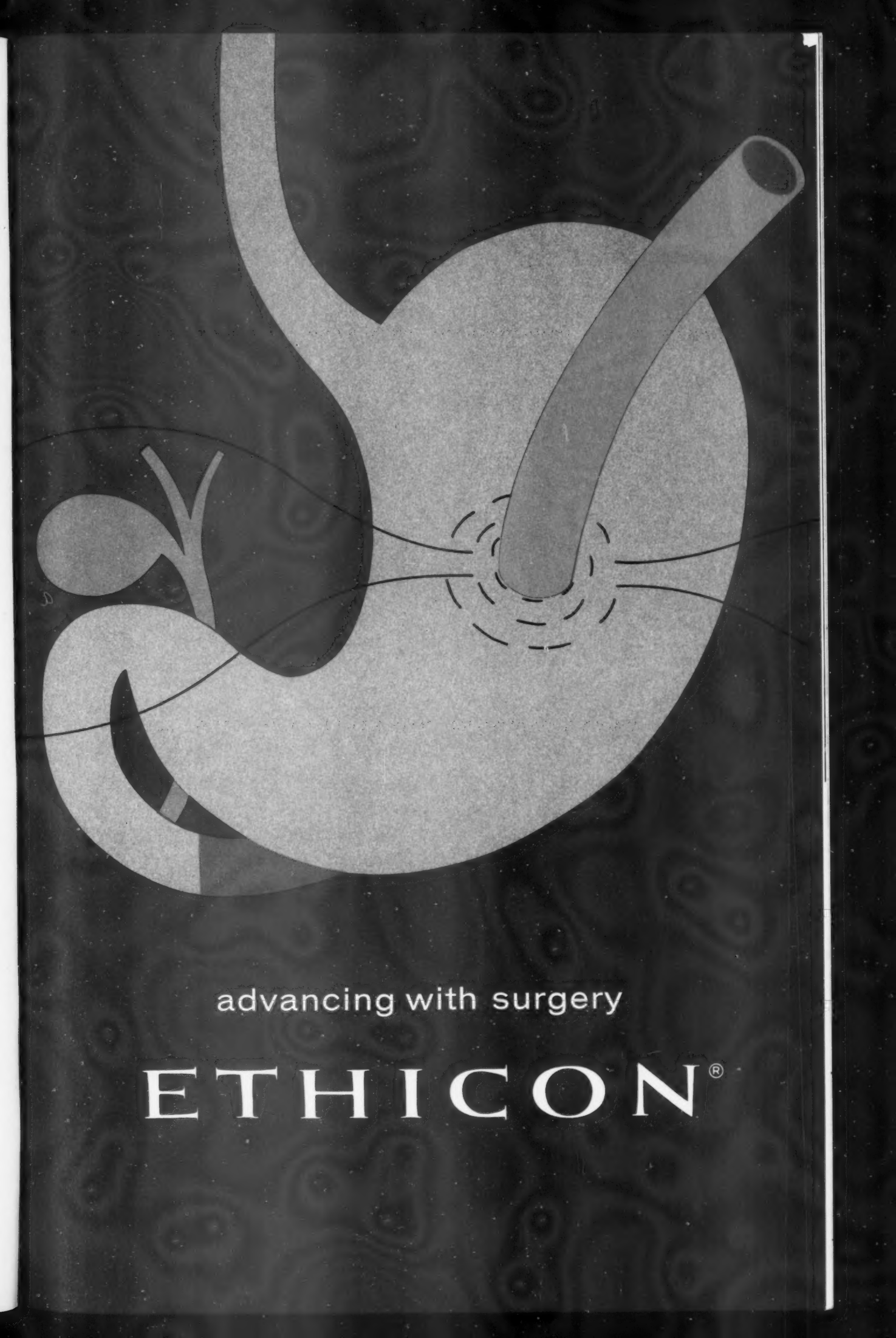
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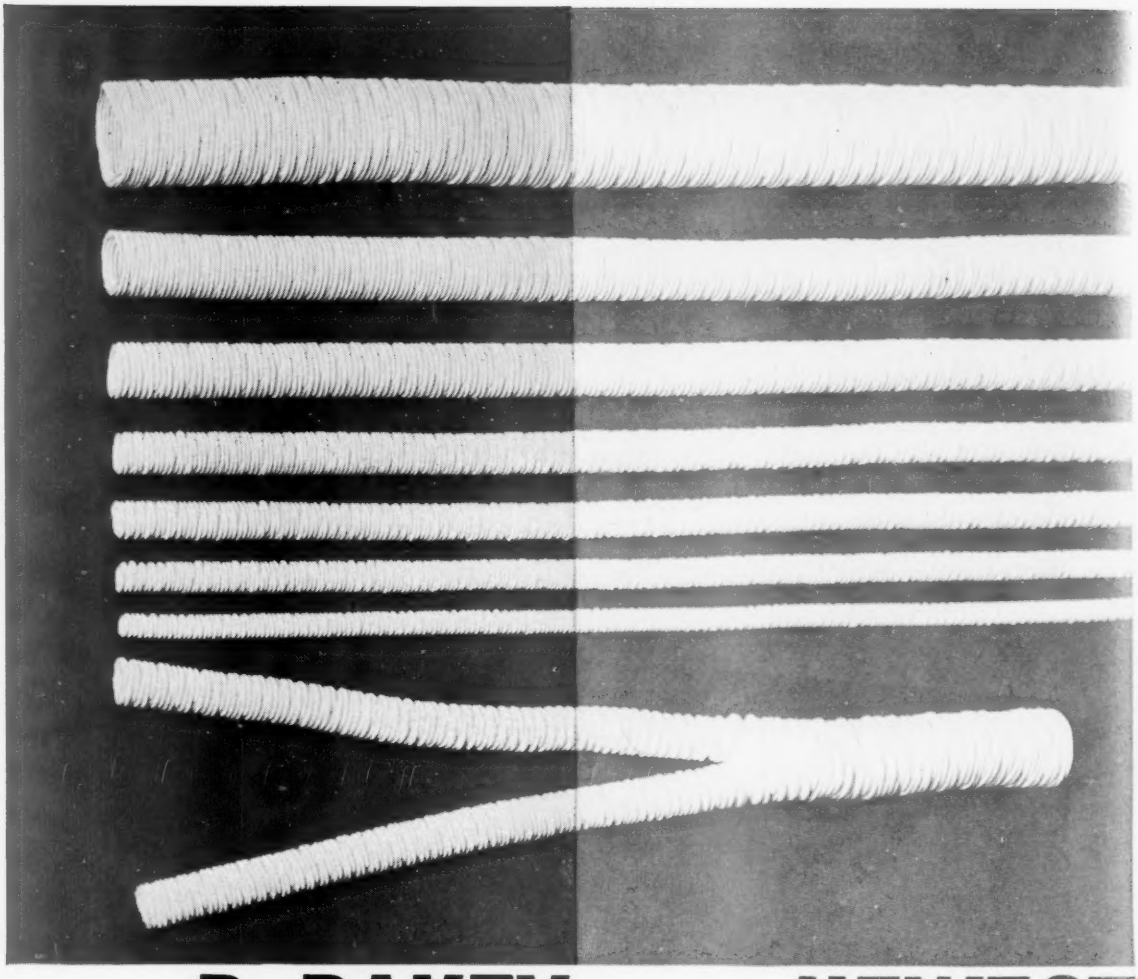

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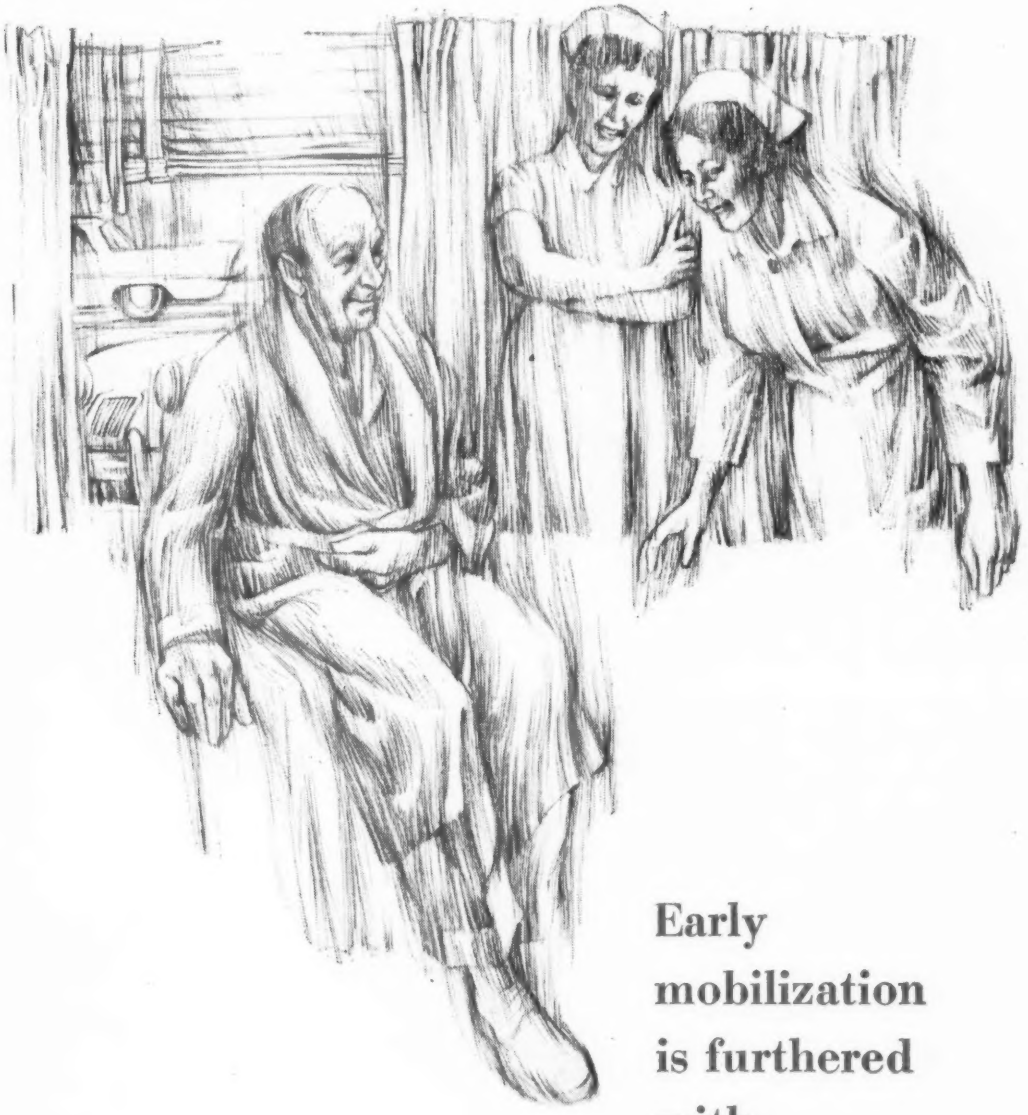

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Ruesch, McI., Miyatake, S. and Ballinger, C.: J.A.M.A., 172:1476, 1960
● From pressure to gravity to pressure with a simple clamp adjustment ● Both hands free to work ● Infuses 500 cc. of blood in 2 to 5 minutes ● Professional Literature Available on Request.
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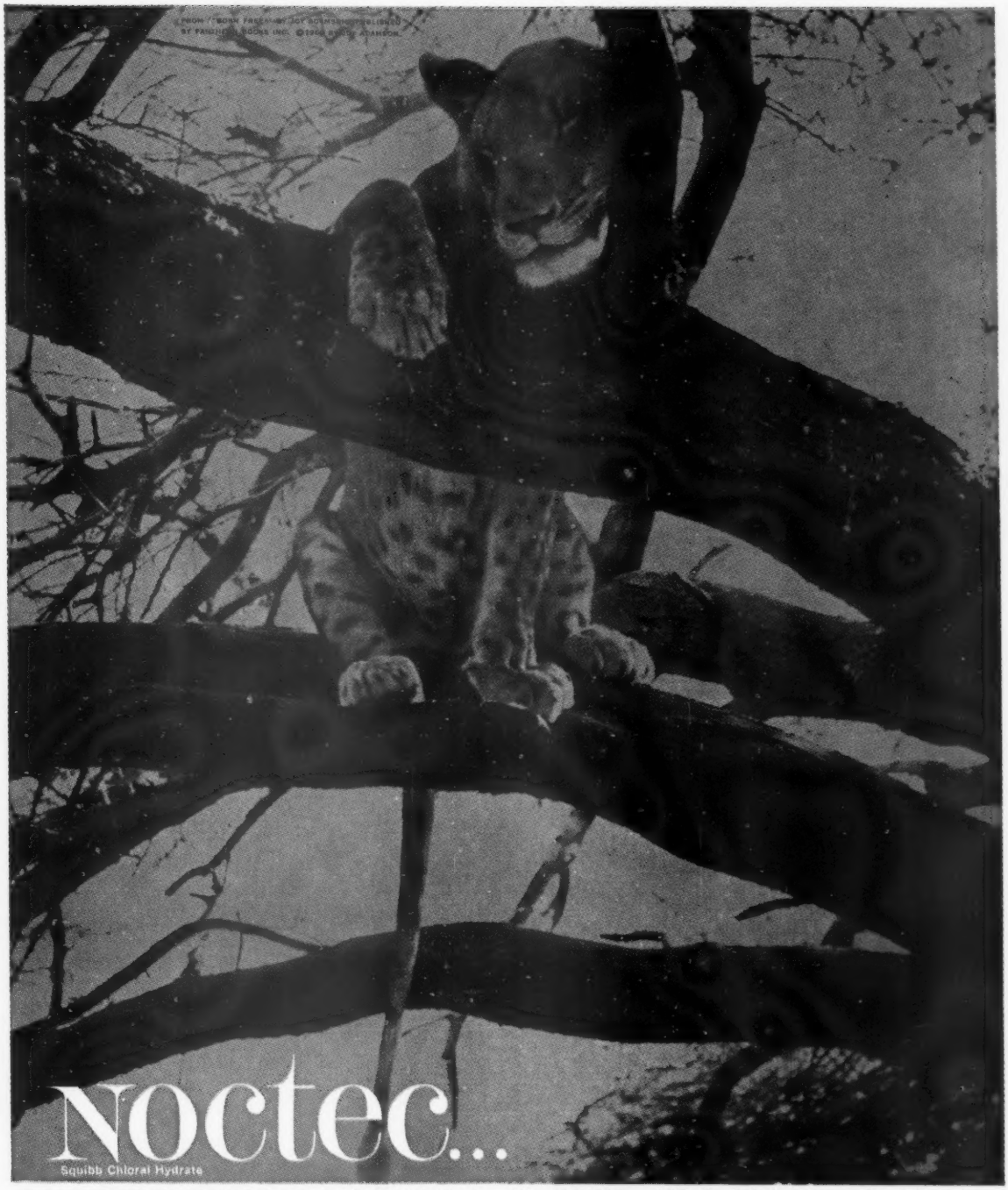

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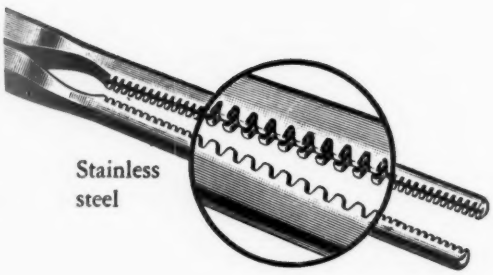

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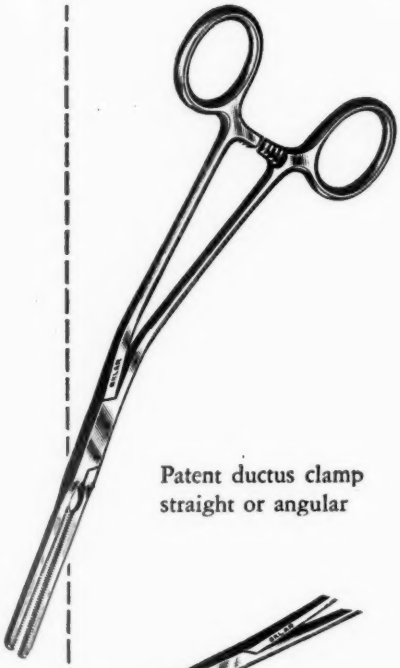
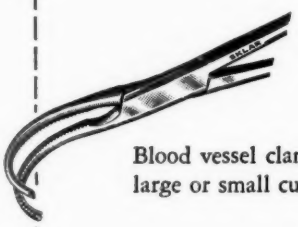


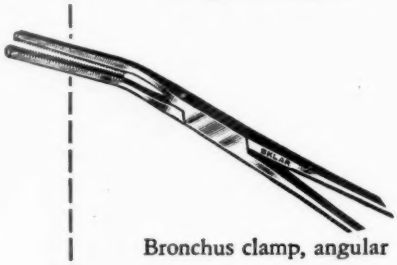
Patent ductus clamp
straight or angular

Satinsky
vena cava clamp



Blood vessel clamp
large or small curve

Coarctation clamp
straight or angular

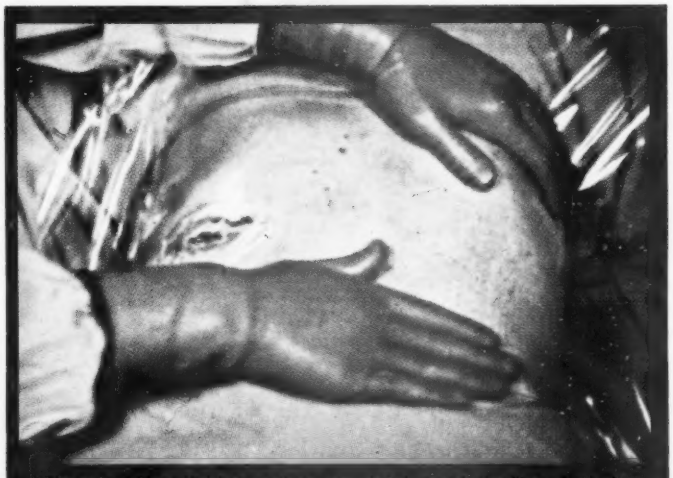


Bronchus clamp, angular

Bulldog clamp
2", 2½" 3", 3½"

"Instead of a skin surface which is merely surgically clean..." **Vi-DRAPE®** Surgical Film *"provides a surface which is completely sterile."*[1]

"A film of sterile transparent plastic is applied to the field. It excludes the skin from the wound as effectively as a surgical glove excludes the bare hands. The incision can be extended or changed."[1] Note close adherence of film to wound edge.



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Isolation of the patient's skin by this bacterial barrier protects the surgical wound, and the surgeon, from the hazard of contamination by the patient's own skin bacteria during the entire operation.

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The original package, to be autoclaved before use, still available in 24" x 42" size.

1. Pace, Wm. G., M.D.: Am. J. Surg. 100:590, Oct. 1960. Reprint sent on request.

2. Walter, Carl W., M.D.: Disinfection of the Skin. Color-sound motion picture, 30 min.-16 mm., sponsored by American Cyanamid, Surgical Products Division and Winthrop Laboratories. Showings arranged through either sponsor.

3. Zollinger, Robt. M., M.D., Pace, Wm. G., M.D., and Reed, M. J., R.N.: A New Transparent Plastic Surgical Drape. Color-sound motion picture, 17 min.-16 mm., produced at Ohio State University, Department of Surgery. Sponsored by and available for showing through Aeroplast Corporation.

Use of Vi-Drape Film is well documented. Please write for reprints. Also, if you would like to see its advantages in various specialties our film described at left[3] is available for showing to your professional group. For descriptive folder with scheduling form, send request to:

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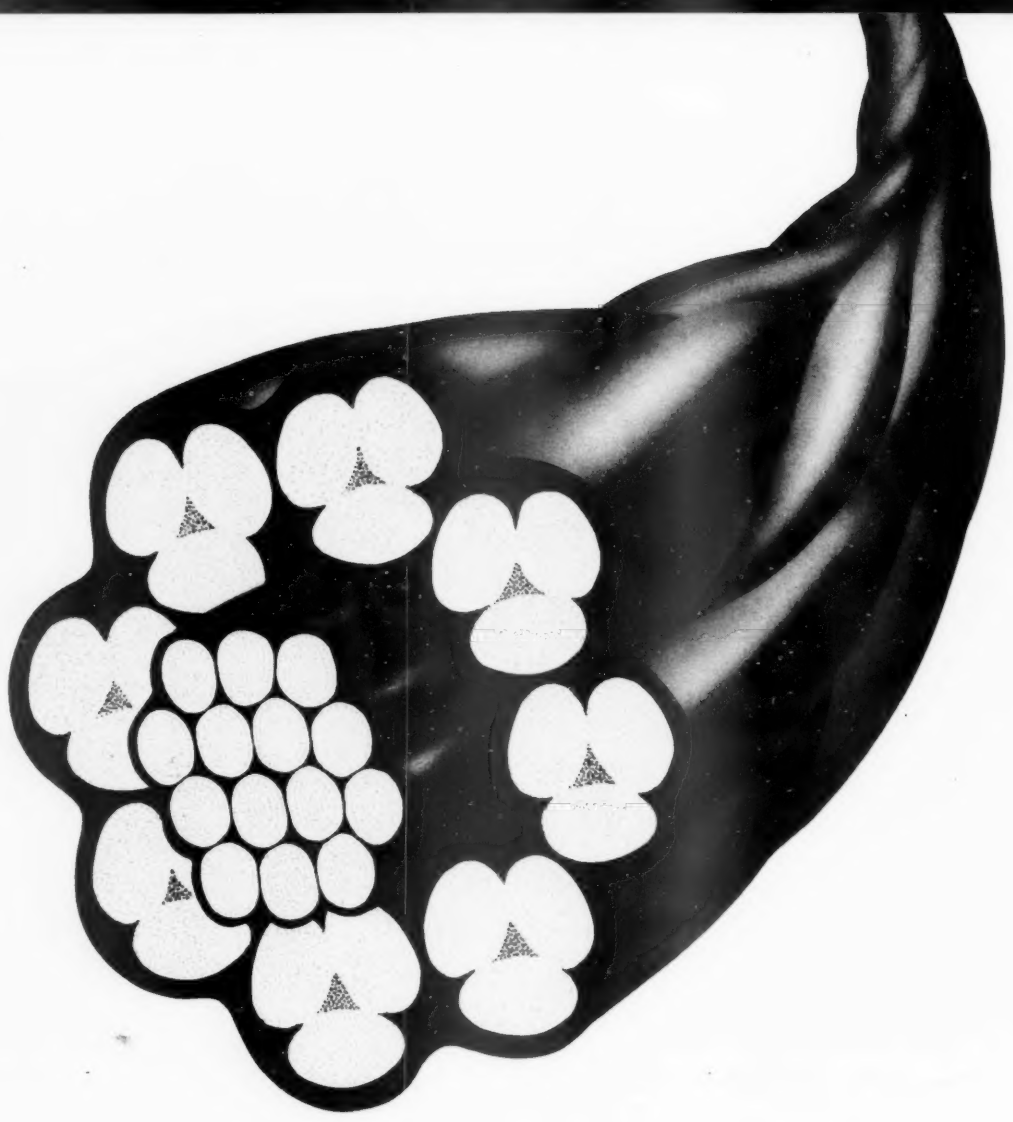

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as hormones alone often don't do

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Calcium Pantothenate	20 mg.

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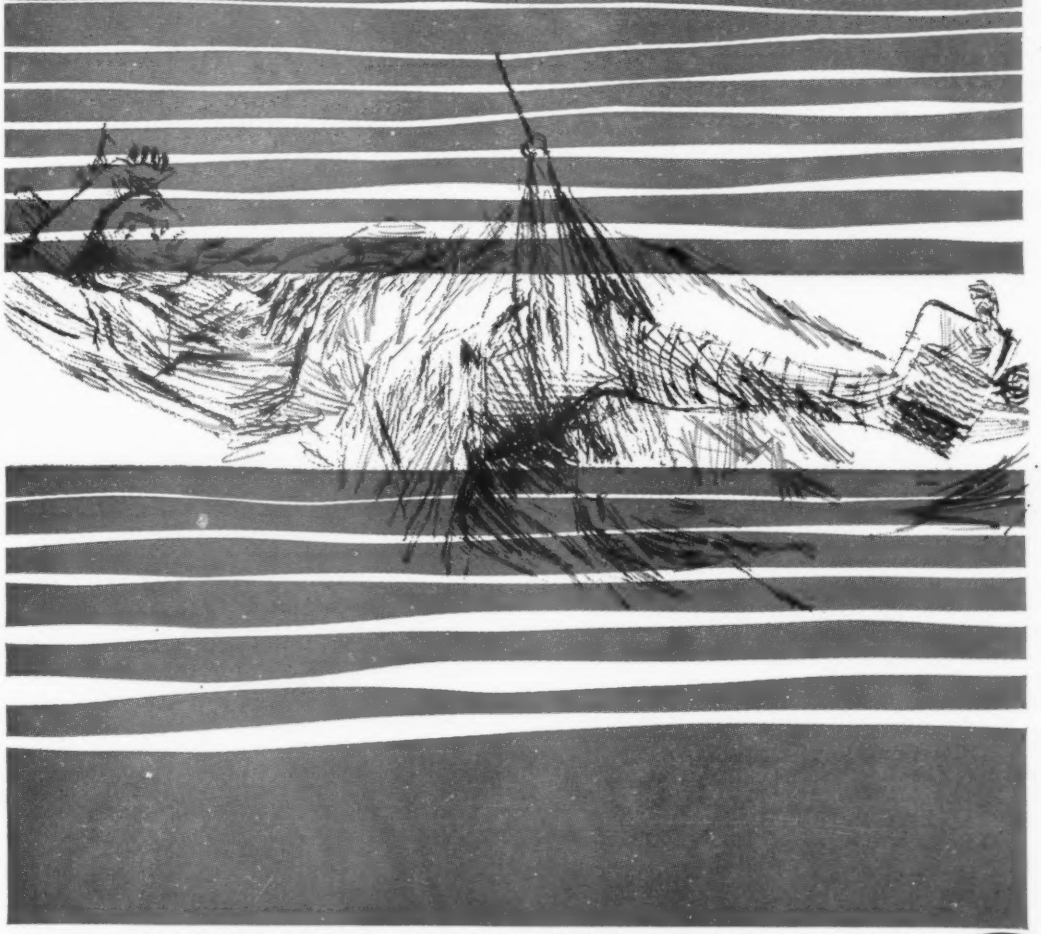

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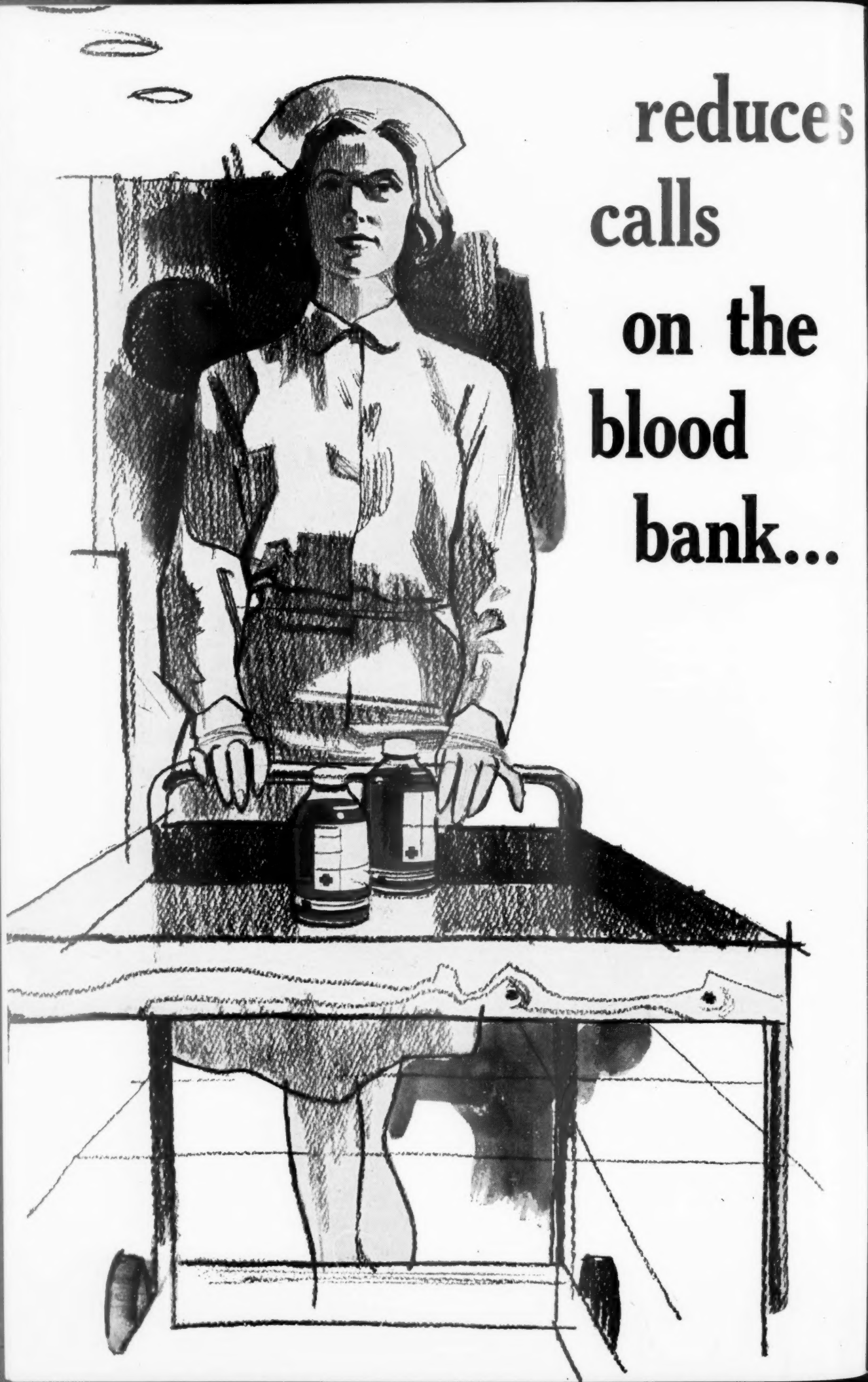
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Adrenosem is indicated pre- and postoperatively in surgery and also nonsurgically to control bleeding associated with vascular pathosis as in peptic ulcer, telangiectasia, purpura, ecchymosis, ulcerative colitis, and others.

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references: 1. Haden, R. L., et al.: Ann. N.Y. Acad. Sc. **49**:641 (May 11) 1948. 2. Cheraskin, E.: J. Am. Dent. Assn. **58**:17 (April) 1959.

*U.S. Pat. Nos. 2581850; 2506294

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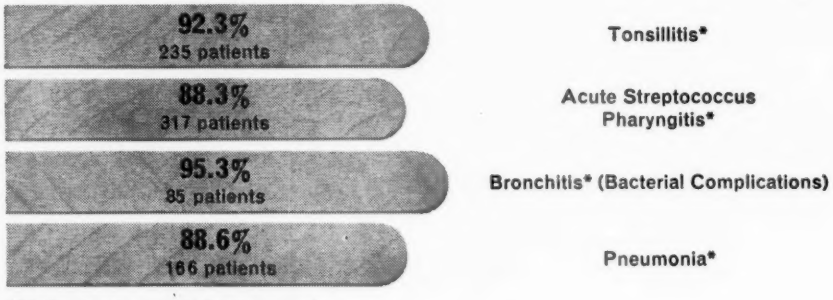

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The usual dosage for infants and for children under twenty-five pounds is 5 mg. per pound every six hours; for children twenty-five to fifty pounds, 125 mg. every six hours.

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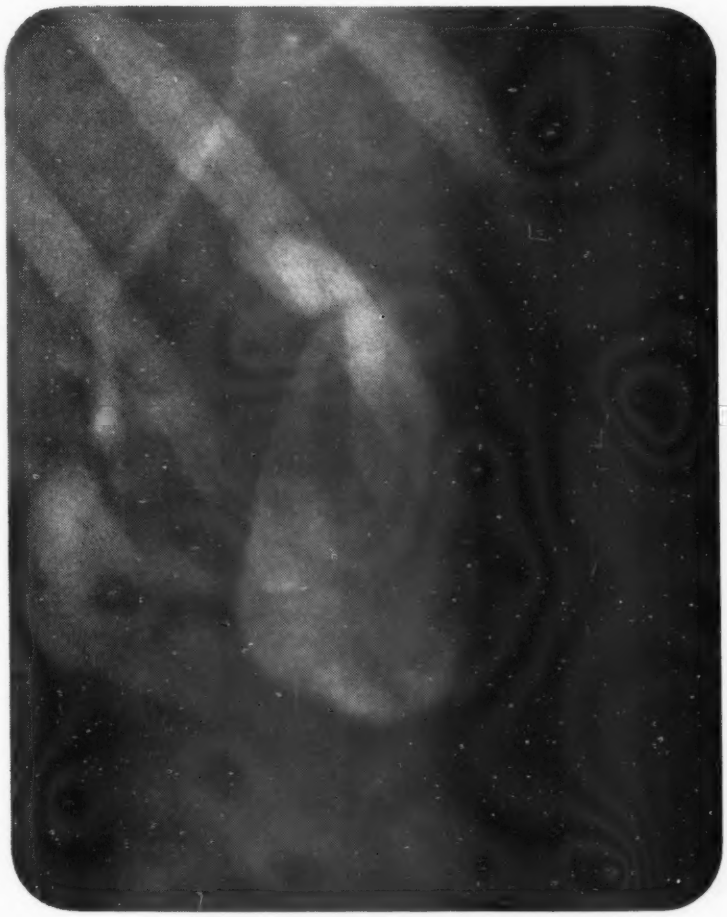

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References: (1) Cohn, E. M.: Am. J. Gastroenterol. *35*:115 (Feb.) 1961. (2) Jones, M. D.; Sakai, H.; and Rogerson, A. G.: J. Pediat. *53*:172 (Aug.) 1958. (3) Machella, T. E.: Gastroenterology *34*:1050 (June) 1958. (4) Orloff, T. L.: Am. J. Roentgenol. *80*:618 (Oct.) 1958. (5) Johnson, G., Jr.; Pearce, C.; and Glenn, F.: Ann. Surg. *152*:91 (July) 1960. (6) McClenahan, J. L.: Pennsylvania M. J. *62*:188 (Feb.) 1959.

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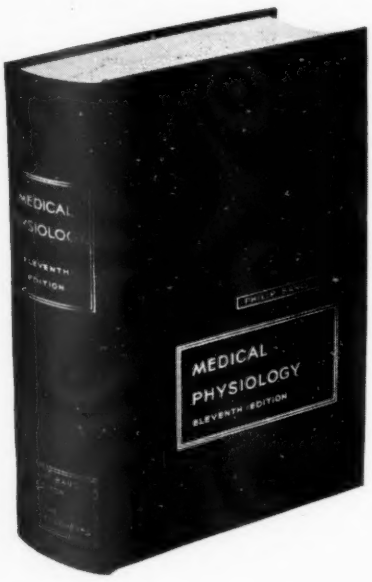

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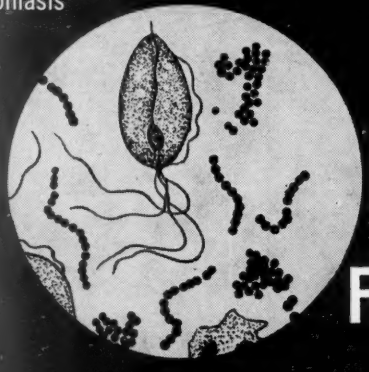
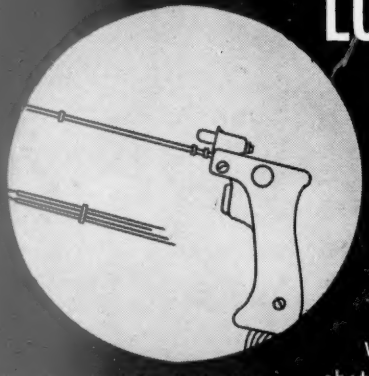


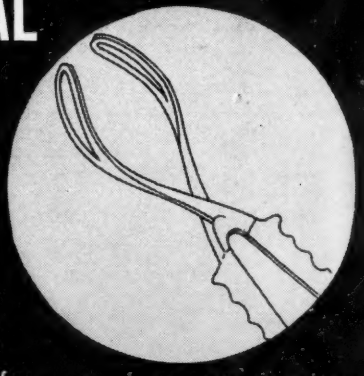
In Nonspecific Vaginitis

NEW WHITE FORMULATION FOR LOCAL CERVICOVAGINAL THERAPY



After Cervical Cauterization, Cervical or Vaginal Surgery

White SULTRIN Cream, formerly available in buff-colored Triple Sulfa Cream, destroys a wide variety of vaginal pathogens and even helps eradicate "difficult" trichomonads by restoring the normal vaginal pH. Outstandingly effective in many obstetric and gynecologic conditions, this triple sulfonamide cream promotes rapid healing, relieves inflammation, minimizes discomfort, and significantly reduces odor and discharge. Supplied: 78 Gm. tube with or without applicator. Also available: SULTRIN Triple Sulfa Vaginal Tablets.



In Postpartum Care

*WHITE FORMULATION

ACTIVE INGREDIENTS: SULFATHIAZOLE 3.42%, SULFACETAMIDE 2.86%, N[1] BENZOYLSULFANILAMIDE 3.7%, AND UREA 0.64%

Ortho